



Results of the public consultation on SCHEER's preliminary opinion SCHEER's preliminary Opinion on electronic cigarettes

A public consultation on this Opinion was opened on the website of the Scientific Committees from 23 September to 26 October 2020.

Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

128 organisations and a number of individuals participated in the public consultation, providing input to different parts of the Opinion, resulting in 691 contributions collected in a table *“Results of the public consultation on SCHEER's preliminary opinion SCHEER's preliminary Opinion on electronic cigarettes.”*

Frequently occurring comments have been answered in a *“Table 1:Frequently occurring comments”* and included issues regarding the lack of comparison with tobacco smoking, the literature search and selection, the risk assessment methodology, the estimation of the risk of second-hand exposure, the delivery of nicotine by e-cigarettes, the lack of recent data on e-cigarette use, and the conclusions on the gateway effect, attractiveness and cessation.

In many cases the Opinion was adapted based on these and other, less frequent, comments, and a selection of the additional literature suggested. A major change in the conclusions was the change of the WoE for the gateway effect from 'strong' to 'moderate' and a change of the WoE for the risk of second-hand exposure from 'weak to moderate' to 'moderate'.

Each submission was carefully considered by the SCHEER and the scientific Opinion has been revised to take account of relevant comments. The literature has been accordingly updated with relevant publications.

The table below shows all comments received on different chapters of the Opinion and SCHEER's response to them. It is also indicated if the comment resulted in a change of the Opinion.



	Frequently occurring comment	SCHEER's response
1	<p>The SCHEER states that e-cigarettes have negative impacts on health, but does not adequately consider these harms in comparison to cigarettes, which is central to public health consideration of e-cigarettes (comparative risk assessment of e-cigarettes and traditional cigarettes and harm reduction). The report ignores the transition from smoking to e-cigarettes use and its benefits to health.</p>	<p>There is no specific mentioning of harm reduction in the specific ToR (Section 2.1). The mentioning of harm reduction in the background is linked to cessation (“their role in harm reduction/cessation of traditional tobacco smoking” – so their role for reducing harm through cessation. There is no stand-alone harm reduction point in these ToR. Therefore, the SCHEER Opinion focuses only on health impacts compared to non-smoking.</p> <p><i>The Opinion was updated highlighting this position in Abstract, Summary, the Scientific Opinion (Section 3) and the Introduction of the Rationale (Section 6.1).</i></p> <p>The substitution of ENDS for cigarette smoking as a viable strategy for improving individual and public health was not within the ToR.</p>
2	<p>Literature search results and selection is incomplete, biased, selective, of poor quality, unbalanced.</p>	<p>The SCHEER refers to the methodology section 4. The search terms used, as well as the search strategies, are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019 until 26 October 2020 (end of the public consultation). In addition, the SCHEER made use of pertinent reports by other organizations on this topic, as well as on information provided by the Commission.</p> <p>Additional literature provided in the public consultation was considered based on these criteria and expert judgment.</p> <p>The literature used was rated according to the WoE procedure of the SCHEER.</p>
3	<p>The SCHEER Opinion provides no real quantification of risk, e.g., in comparison with other benchmarks</p>	<p>Since there are no health based guidance values (HBGVs) for smoking or using electronic cigarettes and existing HBGVs in general are not applicable to the electronic cigarette use scenario, the SCHEER performed a risk assessment in which chemical-specific information that is relevant for the scenario (i.e., intensity, duration, and frequency) is taken into account. Because the available hazard information, often based on animal experiments, will mostly be obtained with an exposure regimen that also will significantly differ from the electronic cigarette use scenario, a direct comparison of exposure and hazard characteristics was considered not to be possible. Human data do not allow a quantitative risk estimation.</p>

		<p>As a pragmatic alternative, the Margin of Exposure (MoE) approach was applied. This approach offers the possibility to take the specific exposure characteristics into account. See for more details Section 6.5.5.2.</p> <p><i>The overall conclusion on the risk remains based on the quantitative level of the MoE.</i></p>
4.	<p>The risks of second hand exposure are overstated.</p> <ul style="list-style-type: none"> - A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids. - The level of absorption of nicotine, PG and VG is such that ambient levels will be low. - Toxicity of the vapour is low, low volumes produced, rapid dispersal in the atmosphere. 	<p>The SCHEER based the risk assessment on the hazard data available and measured ambient air exposure data in model studies and this lead to the overall weak to moderate evidence for a risk of irritative effects, cardiovascular effects and carcinogenic risks, mainly based on low MoEs. The SCHEER acknowledges the fact that the carcinogenic risk is related to the presence of TSNAs in liquids and this only concerns a small proportion of the available liquids.</p> <p><i>The Opinion will be adapted to reflect this low frequency of occurrence of TSNAs, upholding the conclusion of the individual risk to the user.</i></p> <p>Regarding the “low” ambient levels: For each chemical, the exposure concentrations were calculated from the highest amounts exhaled by the volunteers (see table 6), taking into account pulmonary retention (0% for local effects, 50% for systemic effects), that exhalation of the chemical may not have been complete in the first exhalation but may continue with subsequent exhalations, and taking into account ventilation. Using 50% retention for systemic effects can be considered a worst-case default value in view of the much higher alveolar retention of, for instance, nicotine.</p> <p><i>The Opinion is adapted to acknowledge this.</i></p> <p>The risk assessment in the Opinion shows that, indeed, risks are rather limited in view of low exposures. Uncertainties are discussed. The SCHEER cannot agree with the conclusions that taking all the data into account, risks of second-hand exposure are overstated.</p>
5	<p>There is very weak/no evidence that e-cigarettes enhance attractiveness for youth and act as a gateway to (youth) smoking.</p>	<p>SCHEER has taken into account recent European data and results provided by systematic reviews of cohort data. New relevant literature has been cited</p> <p>[1] Chan et al (2020). Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. <i>Addiction</i>. 2020 Sep 4. DOI: 10.1111/add.15246</p> <p>[2] Zhang Y, Bu F, Dong F, et al. The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review</p>

		<p>and meta-analysis. Tobacco Induced Diseases. 2021;19(January):4. doi:10.18332/tid/131624.</p> <p>The opinion was adapted and the weight of evidence was noted as “moderate”.</p>
6.	<p>There is sufficient literature that supports e-cigarettes as smoking cessation tool. The SCHEER opinion missed many observational studies and analyses in Europe on smoking cessation using vaping. The SCHEER approach is very selective and does not reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking and not as a cessation tool.</p>	<p>The SCHEER report has taken into account newer key literature provided in the public consultation which was considered relevant to the report based on the literature search criteria and expert judgment. The main literature included referred to the Cochrane Library Review [1]</p> <p>The Opinion has been adapted to reflect this new literature.</p> <p>[1] Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Fanshawe TR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216.</p> <p>[2] Zhang Y, Bu F, Dong F, et al. The effect of e-cigarettes on smoking cessation and cigarette smoking initiation: An evidence-based rapid review and meta-analysis. Tobacco Induced Diseases. 2021;19(January):4. doi:10.18332/tid/131624.</p>
7.	<p>The SCHEER Opinion only focusses on enhanced attractiveness for youth and potential initiation,.</p> <p>The Opinion does not acknowledge that e-liquid flavors play a significant role in ensuring that smokers fully switch to e-cigarettes and have an important contribution to smoking cessation.</p> <p>The increased product appeal by flavors to adults is essential for their benefit to public health.</p>	<p>Section 6.6 is indeed entitled Role in the initiation of smoking (particularly focusing on young people), as adolescents are a vulnerable group. The SCHEER reviews many reasons for initiation of e-cigarette use in the first part of this section, including curiosity and smoking cessation. Next, the role of flavors is discussed, for different age groups and different smoking status. Regarding flavours, the SCHEER concludes consistent evidence was found that flavours attract both youth and adults to use electronic cigarettes. Flavours decrease harm perceptions and increase willingness to try and initiate use of electronic cigarettes. Adolescents consider flavour the most important e-cigarette attribute in trying electronic cigarettes and were more likely to initiate using through flavoured electronic cigarettes.</p> <p>There are indeed studies that adults who began vaping nontobacco-flavored e-cigarettes were more likely to quit smoking than those who vaped tobacco flavors, such as the one mentioned in many of the comments,</p> <p>[1] Friedman AS, Xu S. Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. JAMA Netw Open. 2020;3(6):e203826.</p>

		<p>However, the authors also acknowledge some limitations: “Critically, this analysis does not establish a causal relationship between flavored e-cigarette use and smoking initiation or cessation. If individuals who want to quit are more likely to choose flavored e-cigarettes, this study’s results could stem from that initial preference. Randomized clinical trials are needed to clarify this relationship. Furthermore, in focusing on the association of vaping with smoking, we did not assess vaping’s health implications in the absence of smoking. More research is needed in that area.”</p>
8.	<p>The SCHEER Opinion is mainly based on US data. Relevant EU data were missed/not included.</p>	<p>Indeed, many publications used by the SCHEER reflect the situation on the US market. Although, the products as well as the liquids used differ frequently between Europe and the US (e.g., with US allowing higher nicotine concentrations with respect to the limit of 20mg/ml nicotine set by TPD in Europe), the SCHEER uses data describing the US market if necessary and tries to draw conclusions for Europe wherever possible. US data may not necessarily reflect the exact situation in the EU, but trends coming from the US frequently also impact European markets.</p> <p>SCHEER also agrees that systematic EU data collection needs to be performed in order to keep up with the rapid evolving e-cigarettes use in the EU market.</p>
9.	<p>Nicotine concentrations of 20mg/ml do not allow for delivery of nicotine that is considered to be comparable to the permitted dose of nicotine derived from a standard cigarette during the time needed to smoke such a cigarette.</p>	<p>The SCHEER agrees that the directive and especially art 20(3) (a, b, g) are meant to limit the risk of accidental poisoning, instead.</p> <p>Furthermore, increasing device power results in increased nicotine yields, and users of e- liquids with low nicotine strength can also achieve the same amount of nicotine per puff as high nicotine liquid users by puffing more intensely. By doing so they may be exposed to higher amounts of toxicants.</p> <p>As we state in the report, “research showed that there is little relationship between nicotine concentration in e-liquids and nicotine concentration in the resulting aerosol, because the composition of the aerosol also depends on the characteristics of the electronic cigarette (temperature, coil, power, ventilation (Goniewicz, et al., 2014; Peace, et al., 2016))”</p> <p>“It is important to note that the upper limit of 20 mg/ml nicotine can be compensated for by technological modifications in the device, yielding similar nicotine emissions levels as the American version that used high nicotine levels in the liquid</p>

		(see below in the section on nicotine) (Mallock, et al., 2020).”
10	There is more evidence on pulmonary toxicity	Indeed, there is a rapidly growing body of evidence derived from in vitro, animal, as well as human studies that e-cigarette use may have significant pulmonary toxicity and impacts pulmonary physiology. Short-term exposure leads to increased airway reactivity, while long-term exposure leads to increased airway resistance, airway obstruction and inflammation. The SCHEER has incorporated the suggested changes regarding pulmonary disease, by adding some relevant review papers and modifying the text accordingly. Nevertheless, the overall conclusion remains unchanged.
11	More recent data need to be included on current and ever use of e-cigarettes	The SCHEER has included the most recent data on the Eurobarometer of 2020, where applicable. However, the 2020 Eurobarometer report presents only descriptive data which are extracted. Within the SCHEER report, we also refer to previous Eurobarometer data (2017) whenever adjusted logistic regression analyses were performed as noted in the peer reviewed literature. Such adjusted analyses have not been performed yet with 2020 data.

1	Name of individual / organisation	Table of contents	Submission	SCHEER's response
1	romeo antonio,jus tgold di romeo antonio raffaele,Italy	2.1. Terms of Reference	2.1 termine di paragone	There is no comment included in this contribution.
2	Poirson Philippe,S ovape,France	2.1. Terms of Reference	[p. 10 l. 16] The term “gateway” refers to a specific causal theory. An explanation is necessary for readers to understand this reference term. Notably the nine scientific criteria that must be met for this concept to be applied to a phenomenon, as presented by Etter (2017). The verification of the adequacy of the theory to these nine criteria should be specified in detail in the report. Without a precise explanation and validation criteria, the term could be confined to a pseudo-science effect.	See Table 1, answer 5.
3	Forconi Valerio,Imperial Brands PLC,Belgium	2.1. Terms of Reference	<p>THE OPINION FAILS TO MEET ITS TERMS OF REFERENCE FOR THE MOST UP-TO-DATE SCIENTIFIC EVIDENCE AND IS OVER-RELIANT ON US DATA</p> <p>The Opinion states “the most recent and up-to-date scientific evidence and technical developments” should be considered when forming a scientific opinion on the highlighted issues. However, the overwhelming majority of recent and relevant research has not been reviewed (see bibliography for a non-exhaustive list). The Opinion considers research published between January 2015 and April 2019, as well as relevant primary sources and literature beyond this period. It is disappointing it does not include a comprehensive review of the more recent scientific literature (essentially there is an 18-month gap in the evidence) and that it is deliberately selective in its chosen references (as outlined in this submission). A notable omission is the UK Royal College of Physician’s comprehensive report on e-cigarettes[1]. SCHEER’s conclusions are therefore based on a narrow selection of the available literature (not the totality thereof) and does not accurately reflect either the relative risk of e-cigarettes compared to smoked tobacco, or their benefits</p>	See Table 1, answer 8.
				See Table 1, answer 2.
				See Table 1, answer 1 .

in the context of tobacco harm reduction for adult smokers who transition. This is exemplified by the ubiquitous terminology applied (i.e. ‘user’) which fails to accurately define individual groups, whether adult smokers, dual users (who are transitioning to exclusive e-cigarette use), current e-cigarette users, never-smokers, young people, and legally defined youth. This is not only confusing but may lead to confusion and inappropriate conclusions about the current state-of-play, particularly amongst youth. More information is included in our response below.

4 O’Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy

2.1. Terms of Reference

The Terms of Reference did not call for the evaluation of the substitution of ENDS for cigarette smoking as a viable strategy for improving individual and public health. A staggeringly high number of EU adults who smoke have no intention to quit. Country No intention to quit Germany 42.4%; Greece 59.5%; Hungary 68.1%; Netherlands 18.9%; Poland 58.7%; Romania 46.4% Spain 63.5%

See Table 1, answer 1.

From Hummel et al. 2018. It is critically important to consider the evidence statement by the National Academies of Science, Engineering, and Medicine: “There is substantial evidence that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes.” For example, testing by Goniewicz et al. (2014) found that ENDS toxicant emissions are 9 to 450 times lower than in cigarette smoke. Furthermore, many toxic substances in cigarettes are not emitted by ENDS. For example, ENDS emissions testing by Marco and Grimalt (2015) did not detect 61 of 79 compounds present in tobacco smoke (tally of Table 1). These data are corroborated in the systematic review by the European Respiratory Society (Bals et al., 2019) and other reviews (Traboulsi et al., 2020; Wang et al., 2019). Stephens (2018) calculated the cancer potency of ENDS to have 0.004 of the relative lifetime cancer risk of tobacco smoke.

ENDS substitution for individuals who smoke has demonstrated positive health benefits in clinical studies. A randomized controlled trial of ENDS substitution for cigarette smoking demonstrated that

after one month of biochemically verified substitution, chronic smokers had significant improvements in their vascular health (George et al., 2019). A 6 month clinical assessment of exclusive ENDS users with asthma showed significant improvements in controlling their symptoms (Solinas et al., 2020). A five year assessment of patients with congestive obstructive pulmonary disease (COPD) documented that those switching to ENDS use had better health outcomes than those who continued to smoke (Polosa et al., 2020).

A positive effect of ENDS substitution is also predicted for population health. A review on nicotine addiction treatment by Prochaska and Benowitz (2019), leading expert researchers on tobacco, state “While e-cigarettes may have adverse effects on respiratory health and possibly other diseases, the harm is generally accepted to be much less than that of cigarette smoking. Thus, if smokers were to switch completely to e-cigarettes, then smoking-related disease is predicted to decrease substantially. Population-based models of the impact of e-cigarette use predict an overall health benefit” (pp. 17-18).

The potential benefits of ENDS substitution for cigarette smoking on individual and population health certainly merit its evaluation.

P10 L16-17 The gateway hypothesis is not the only explanation for a correlation between youth ENDS and cigarette use (National Academies of Science, Engineering and Medicine, 2018; WHO Study Group on Tobacco Product Regulation, 2019). The common liabilities theory posits that a “common latent propensity to risky behaviour” (WHO, 2019, p. 57, see also Owotomo et al., 2018) that leads to concurrent cigarette and ENDS use. The European Respiratory Society states that shared risk factors are “likely alternative explanations supported by the literature” (Bals et al. 2019, p 14; see also Chan et al., 2020). Hammond et al. (2017) in a one year longitudinal cohort study (Canada, N=19,130) state that “it is highly plausible that ‘common factors’ account for a substantial proportion of increased cigarette-smoking initiation among e-cigarette users” (p. E1135). The common liabilities hypothesis should be evaluated.

References:

Bals, R., Boyd, J., Esposito, S., Foronjy, R., Hiemstra, P. S., Jiménez-Ruiz, C. A., ... & Spira, A. (2019). Electronic cigarettes: a task force report from the European Respiratory Society. *European Respiratory Journal*, 53(2).

Chan, G. C., Stjepanovic, D., Lim, C., Sun, T., Shanmuga Anandan, A., Connor, J. P., ... & Leung, J. (2020). Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*, online publication September 4.

George, J., Hussain, M., Vadiveloo, T., Ireland, S., Hopkinson, P., Struthers, A. D., ... & Lang, C. C. (2019). Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes. *Journal of the American College of Cardiology*, 74(25), 3112-3120.

Hammond, D., Reid, J. L., Cole, A. G., & Leatherdale, S. T. (2017). Electronic cigarette use and smoking initiation among youth: a longitudinal cohort study. *Canadian Medical Association Journal*, 189(43), E1328-E1336.

Marco, E., & Grimalt, J. O. (2015). A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers. *Journal of Chromatography A*, 1410, 51-59.

Owotomo, O., Maslowsky, J., & Loukas, A. (2018). Perceptions of the harm and addictiveness of conventional cigarette smoking among adolescent e-cigarette users. *Journal of Adolescent Health*, 62(1), 87-93.

Polosa, R., Morjaria, J. B., Prosperini, U., Busà, B., Pennisi, A., Malerba, M., ... & Caponnetto, P. (2020). COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Therapeutic Advances in Chronic Disease*, 11, 2040622320961617.

Prochaska, J. J., & Benowitz, N. L. (2019). Current advances in research in treatment and recovery: Nicotine addiction. *Science Advances*, 5(10), eaay9763.

Solinas, A., Paoletti, G., Firinu, D., Di Pino, M., Tusconi, M., Mura, J. F., ... & Marongiu, F. (2020). Vaping effects on asthma: results from a web survey and clinical investigation. *Internal and Emergency Medicine*, 1-9.

Traboulsi, H., Cherian, M., Abou Rjeili, M., Preteroti, M., Bourbeau, J., Smith, B. M., ... & Baglolle, C. J. (2020). Inhalation Toxicology of Vaping Products and Implications for Pulmonary Health. *International Journal of Molecular Sciences*, 21(10), 3495.

WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group. Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1015). Chapter 3.

5	Compernelle Thomas, British American Tobacco, Belgium	2.1. Terms of Reference	As set out in Section 2 concerning SCHEER's mandate, this SCHEER Opinion is of specific significance because it will have a direct impact on the legislative work for the adaptation of the Tobacco Products Directive. The final report will form the scientific basis for legislation for 450 million consumers and it is, therefore, of particular importance that it is of the highest scientific quality. According to SCHEER's Rules of Procedure the objective of the public consultation is to enhance the quality of the final work
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and BAT encourages SCHEER to consider all comments carefully with that objective in mind.

SCHEER should further ensure that its final opinion adequately addresses the Terms of Reference, is compliant with its Rules of Procedure and follows the approach set out in its 2018 Memorandum on weight of evidence and uncertainties.

In this respect we note that the Preliminary Opinion should but does not meaningfully address the potential positive health benefits for EU adult smokers using e-cigarettes as alternatives to smoking, ignoring the public health principle of tobacco harm reduction. Without taking these into account, SCHEER cannot adequately address the terms of reference, both in terms of addressing considerations relevant both at an individual level and at a population level from a public health perspective (which must include smokers), as specifically required under the terms of reference, and in providing the required scientific analysis to assess the potential need for legislative amendments.

See Table 1, answer 1.

SCHEER state that e-cigarettes have negative impacts on health, but does not adequately consider these harms in comparison to cigarettes, which is central to public health consideration of e-cigarettes. SCHEER should do so and cannot disregard a growing body of international and independent scientific evidence that exclusive use of e-cigarettes reduces users' exposures to toxicants, and that e-cigarettes are an effective component of a tobacco harm reduction strategy. The assessment should focus on the balance of risks between smoking and vaping and how this affects EU public health considering transitions between smokers, vapers and non-users.

The Preliminary Opinion does not adequately address the EU context as called for under the mandate and the Terms of Reference. Data derived from studies with either outdated products or only those available outside the EU are included. Risks are discussed in the report based on non-EU and pre-TPD products and are therefore not relevant in this context as these e-liquids are not currently available in the EU. This does not meet the main purpose of the

See Table 1, answer 2.

opinion “to assist the Commission in assessing the most recent scientific and technical information on e-cigarettes.”

SCHEER’s selective and limited presentation of the evidence and its lack of disclosure of its assessment of evidence does not meet the required standards of scientific advice set out in the Rules of Procedure and the approach stated in the 2018 Memorandum on weight of evidence and uncertainties. A large body of scientific evidence has not been considered by SCHEER, in particular the most recent scientific information. This lack of transparency and incomplete review of the evidence raises a question as to the reliability of the report. SCHEER should address this and in any event disclose the criteria used to select the scientific literature and also the methodology to evaluate the strength of the scientific information to inform this Opinion.

See Table 1, answer 8.

In light of the significance of the report such methodological problems should be rectified in the final version and any preliminary findings affected by these methodological problems should be reassessed.

6 Woessner 2.1. Terms of
Julie, Intern Reference
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Nicotine
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(INNCO),
Swiss
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association
with 35
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over the
world and
15 from
the EU

Page 10 / Lines 21-22
Most recent and up-to-date research is important, but a great deal of research was not included that is not only relevant, but critical to any substantive analysis of electronic cigarettes. SCHEER consistently fails to include data that compares electronic cigarettes to smoking which is a remarkable exclusion given that the vast majority of vapers (electronic cigarette users) are either former smokers or are in the process of reducing their smoking habit. Risk assessment is imperative, including not only comparisons to smoking, but also framing risks in terms of, for example, everyday activities.

See Table 1, answer 1.

In a global public health perspective, as stated by SCHEER, it’s important to consider vulnerable populations and other populations. The risk assessment should balance the different risks. The wide use of US evidence by the SCHEER seems to have led its preliminary Opinion in one direction only. Lauren et al., 2019 clearly stated how the formulation of the question influences the debates: “Fundamentally, the 2 reports differed on whose risk was

to be given priority. For PHE, the central public health concern was how to protect the health of current smokers. For the United States, the pivotal issue was the protection of children and non-smokers—innocent bystanders. The formulation of the questions and inclusion and exclusion criteria is always a value-based process.”

Ref:

Laureen et al. (2019). The E-Cigarette Debate: What Counts as Evidence? *AJPH* July 2019, Vol 109, No. 7. doi: 10.2105/AJPH.2019.305107

7	No agreement to disclose personal data	2.2. Deadline	<p>SCHEER SHOULD HAVE PERMITTED MORE TIME FOR STAKEHOLDERS TO RESPOND</p> <p>Given that SCHEER produced the 176-page Opinion over a period of at least 18-months it is difficult to understand why stakeholders and other parties are allowed less than 30 days to officially respond to a report produced for EU COM to aid key policy-making decisions. Moreover, the template is not user friendly and it only allows a limited number of characters to provide a comprehensive analysis of the totality of scientific evidence on e-cigarettes and stakeholder views on this very complex matter.</p>	<p>The public consultation for the preliminary Opinion on e-cigarettes was open from 23 September until 26 October 2020, i.e. for almost 5 weeks. This is in line with the Rules of Procedure of the scientific committees¹, ANNEX V-STAKEHOLDER DIALOGUE PROCEDURES: “Public consultation shall be open for a minimum period of 4 weeks”.</p>
8	Olteanu Vlad, Juul Labs Inc., Belgium	6.1 Introduction/Definition	<p>Lines 26 and 27 of the Opinion, under this heading, state that “This Opinion is restricted to the terms of references given by the European Commission. It covers electronic cigarette products complying with the TPD.” With that stated criteria, SCHEER should have limited the evidence it used, as well as the scope of its analysis, to e-cigarettes that fully comply with the TPD requirements. Instead, SCHEER included data referring to e-cigarettes containing nicotine concentrations higher than 20mg/ml or e-cigarettes that (because of their technical characteristics) are otherwise non-compliant with TPD requirements. In fact, data from Member States regulatory authorities reviewing electronic cigarettes compliant with TPD requirements and marketed in their territories were not reviewed by SCHEER (such is the case for the Public Health England Study (PHE 2020) uploaded under this heading). We would invite SCHEER to not only use the mandated relevant data in its analysis, but also to exclude irrelevant data and to use the relevant data to its full extent.</p> <p>Ref: GOV.UK. Vaping in England: 2020 evidence update summary</p>	<p>See Table 1, answers 8 and 11.</p>

¹ https://ec.europa.eu/health/sites/health/files/scientific_committees/docs/rules_procedure_2016_en.pdf

9	<p>Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU</p>	<p>6.1 Introduction/Definition</p>	<p>Page 20 / Line 5-7 The SCHEER should remove “simulate tobacco cigarettes”. The phrase “simulate tobacco cigarettes” is contained nowhere in the referenced source, Breland et al., 2017. Page 20 / Line 20 The phrase “inhale a liquid” is misleading. The SCHEER should replace it with “inhale an aerosol created through the heating of a liquid”. The remainder of the sentence “that may contain nicotine and/or other chemicals” should be changed, too, as it refers to products not containing nicotine. As stated on the same page (lines 27-28): “Electronic cigarettes not containing nicotine are not addressed in this Opinion.”</p> <p>Page 20 / Lines 22-24 The referenced source (Cobb et al., 2011) seems completely inapplicable to the statement for which it is referenced. Moreover, this sentence misleadingly states that vaping devices produce “smoke”. The SCHEER should replace the whole sentence with: “Vaping devices have been invented to replace tobacco smoking with a cleaner nicotine delivery system that keeps concomitant motor and sensory stimulation, including hand-to-mouth movement and visible aerosol production to ease the switch from smoking.”</p> <p>Page 20 / Lines 26-31 This part should be placed first in the Introduction/Definitions section as it defines the scope of the Opinion. If this Opinion covers only products sold in the EU, it shouldn’t consider evidence based on non-EU products or, at least, clearly state for each risk assessment the part of evidence based on EU products/populations and the part of evidence from outside the EU. It should also be clearly assessed for each risk the value of non-EU data.</p>	<p>The Opinion has been changed in line with the text proposed. Although this opinion does not cover electronic cigarettes not containing nicotine, the description of the devices is not changed.</p> <p>See table 1, answer 8.</p>
10	<p>No agreement to disclose personal data</p>	<p>6.2. Design Features</p>	<p>The opinion should include a recommendation on the importance of defining specific production standards for both liquids and devices in order to avoid the ambiguity of residual toxicity.</p> <p>That should be done involving also the producers in any EU commissions, in order to emit clear production rules for liquids and devices.</p>	<p>It is for the policy makers to provide such a recommendation (risk management). Please see Chapter 6.3. in the final Opinion.</p>

11	No agreement to disclose personal data	6.2. Design Features	pag. 21, line 43-47 The opinion should include a recommendation on the importance of defining specific production standards for both liquids and devices in order to avoid the ambiguity of residual toxicity. That should be done involving also the producers in any EU commissions, in order to emit clear production rules for liquids and devices.	Please see the response to comment 10.
12	Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.2. Design Features	P. 20 l. 46 We suggest inserting the word “may” after the word “reactions” because under normal operating temperatures chemical reactions leading to degradation products do not happen. Such reactions only take place when the e-liquid is overheated.	The text of the Opinion has been changed to:” In addition, high temperature driven chemical reactions occur (Visser <i>et al.</i> , 2014 and 2015; see also table 3).”
13	No agreement to disclose personal data	6.2. Design Features	<p data-bbox="539 600 1256 751">EU REGULATORS SHOULD ENSURE THE DESIGN FEATURES OF E-CIGARETTES PROTECT AGAINST TAMPERING AND ADULTERATION: CLOSED- SYSTEM DEVICES OFFER AN ENHANCED PRODUCT DESIGN AND SAFETY PROFILE OVER OPEN-SYSTEM PRODUCTS</p> <p data-bbox="539 791 1256 1094">The e-cigarette category is not homogenous, and the Opinion fails to highlight which studies refer to closed-system or open-system e-cigarette products specifically. The current design features of open-system devices provide maximum opportunity for individual customisation and can be used to deliver illicit substances, including DIY liquids and/or liquids acquired from unknown or unregulated sources. As such, open-systems can be modified in ways that could increase their potential for harm, presenting the greatest opportunity to modify aerosols and potentially, their harm profile.</p> <p data-bbox="539 1126 1256 1374">Open-system e-cigarettes models can be customised mechanically by users to increase power, which can increase nicotine yields. Variable and increased voltage open system e-cigarettes can deliver increased nicotine concentrations and are able to exceed the nicotine delivery profiles of tobacco cigarettes, even when using low nicotine strength liquids[1]. Thus, open- system e-cigarettes may have implications for abuse liability and should be closely monitored.</p>	<p data-bbox="1285 791 1621 815">No change of the text is needed.</p> <p data-bbox="1285 823 2136 903">Open- & closed systems are well referenced with studies, Breland <i>et al.</i>, 2017 The further details are referred to in the opinion wherever a particular study/ studies is/ are referenced.</p>

IMB believes regulatory measures should limit the ability for users to alter the generated aerosol and flavour ingredients. This was unfortunately demonstrated recently in the US, where Federal and State scientists found illicit tetrahydrocannabinol (THC)-containing e-cigarettes (not regular nicotine-containing products) with vitamin E acetate (used as a thickening agent) were responsible for more than 350 lung illnesses. In response, the US Centers for Disease Control and Prevention recommended: “not [to] modify e-cigarette products or add any substances to these products that are not intended by the manufacturer.” IMB fully endorsed this message and believes regulatory measures should be applied to limit the ability for users to alter the generated aerosol or add ingredients not intended by the manufacturer.

This has already been discussed in the section 6.2. Design Features.

Closed-system, pod-based devices can help ensure both the flavour ingredients and the generated aerosol fall within pre-defined and regulated EU standards. Closed-systems offer an enhanced product quality profile over other e-cigarette devices and the most consistent vaping proposition for adult smokers. To boost consumer trust in product quality and safety, regulatory measures that improve product quality, safety and manufacturing standards should be considered to limit opportunities for e-cigarettes to be adulterated and abused.

This aspect is out of the scope of the current mandate for risk assessment.

Thank you for the comment. Precaution measures have been outlined in the opinion, section Electronic cigarettes and injuries due to burns and explosions.

BATTERY STANDARDS: Closed pod-based vape systems use standard lithium-ion batteries that are safe if users follow the consumer guidance. We also draw the SCHEER’s attention to sensible guidance such as those issued by the UK Fire Brigade[2] and UK Government[3].The EU should ensure that all vape products meet relevant electrical safety standards. At a minimum, the EU should ensure all devices are CE certified and assessed by an independent third party to comply with:

1. General Product Safety Directive
2. Restriction of Hazardous Substances Directive
3. Low Voltage Directive
4. Electromagnetic Compatibility Directive
5. Battery Safety Standard

The EU should also mandate all e-cigarettes contain safety features that protect against overvoltage and overheating, which is currently

The Opinion has been amended.

not the case for all open-systems on the EU market. Consumers should be made aware of the risks associated with the use of non-EU notified and inferior quality vape products, which should not be made available for EU consumers.

References :

Talih, S., Balhas, Z., Eissenberg, T., Salman, R., Karaoghlanian, N., El Hellani, A., Baalbaki, R., Shihadeh, A. (2015). Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine & Tobacco Research*, 17(2), 150-157.

Brown CJ, Cheng JM (2014) Electronic cigarettes: product characterisation and design considerations *Tobacco control* 23 Suppl 2: ii4-10 doi:10.1136/tobaccocontrol-2013051476

Wagener TL et al. (2016) Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third generation electronic cigarette users *Tobacco control* doi:10.1136/tobaccocontrol-2016053041

St Helen G, Havel C, Dempsey D, Jacob P, 3rd, Benowitz NL (2015) Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes *Addiction* (Abingdon, England) doi:10.1111/add.13183

<https://www.london-fire.gov.uk/safety/the-home/smoking/vaping-and-ecigarettes/>
<https://www.gov.uk/government/news/take-charge-of-battery-safety-when-using-e-cigarettes>

14 Waclaw Michalina, Prawo dla Ludzi (Law for People), Poland

6.2. Design Features

The consulted report has a specific purpose. It is to provide decision-makers with information that will help in a reliable assessment of e-cigarettes products. It has to translate scientific research into political language. The language it is written in, biased expressions, and the lack of reliable analysis make it fail to meet this goal. An example of this is the statement "e-cigarettes can cause cancer" without further specifying likelihood, risk or otherwise. Such a statement is unscientific and useless for policymakers, its scope is too wide. Moreover, it is formulated in such a way that it is prejudiced and creates anxiety around the products. At the same time, reports that were omitted from the SHEER publication show evidence that e-cigarettes are up to 95% less harmful than traditional cigarettes.

The SCHEER does not state that “e-cigarettes can cause cancer” in the Opinion.

A detailed analysis of human evidence for health impacts of electronic cigarettes is given in para 6.5.4. In the opinion the evidence for carcinogenicity is specified for e-cigarette users as well as for bystander.

15 Bamberger Claude, Aide, France

6.2. Design Features

p21 L26 this statement about market share is false and has been shown to be for a long time as it is sourced from a US business review of sales in places selling tobacco cigarettes (Nielsen survey data of convenience stores and gas stations), not in specialized shops or online.

The text of the Opinion has been amended as follows: to” with the **large** US market share 25 (~75% as of 2019 and growing notable for their popularity among teens)

			<p>p21 L35 Pretending that higher nicotine levels are/were not accessible is also false and still is as many brands in the US carry comparable refillable e-liquid (salted, or not). And 36mg/ml refills (or pre-filled) were common even nearly a decade ago and it is only in the EU that this ended.</p> <p>It is very strange that nowhere in this report this difference is studied in terms of smokers who failed to switch because of those limitation in the EU (mandate : "their role in harm reduction / cessation of 26 traditional tobacco smoking")</p>	<p>The Opinion says the opposite –the studies on switching from tobacco cigarettes (TC) to e-cigarettes are presented in the Opinion.</p> <p>The summary of this opinion, page 8, item 3. Clearly underline the finding:” In the EU, research has indicated that from current and former smokers, the number of those who had ever attempted to quit without assistance increased from 70.3% in 2012 to 74.8% in 2017 and to 76% in 2020. During this timeframe, use of electronic cigarettes for smoking cessation increased (3.7% to 9.7% to 11%).</p>
16	Olteanu Vlad,Juul Labs Inc.,Belgium	6.2. Design Features	<p>This section is completely inadequate in its description of e-cigarette features and their evolution. A third of the content (Page 21, Lines 25-37) is dedicated to a single US product in a category that boasts several sub-categories and hundreds of brands. In addition, there is no acknowledgement of the intended purpose of e-cigarette evolution and innovation –that is to deliver nicotine in a manner that is competitive with a combustible cigarette and in a way that exposes the user to less toxicants.</p> <p>There is no discussion of the fact that key features of newer e-cigarettes, including the US ‘pod-mod’ described, have been demonstrated to result in lower carbonyl yields compared to other previously studied e-cigarettes, on average, and combustible cigarettes by an order of 10-1000 (Talih el. 2019) .As mentioned, a third of this section is dedicated to a single brand of e-cigarette, and the text used (page 21, lines 25-37) is nearly identical to the fourth paragraph of Strongin 2019, a review on e-cigarette chemistry and analytic detection and should be cited as such. Moreover this is a description of a device combination that is not TPD-compliant and does not exist in the European Union. SCHEER page 21: “It should be noted, that the electronic cigarette brand with the largest US market share (~75% as of 2019 and growing notable for their popularity among teens) is an electronic cigarette that uses changeable, nicotine salt-based liquid cartridges and temperature regulation to produce an aerosol as an alternative to traditional cigarettes. This type of electronic cigarette does not fall into any of the four generation classifications, but rather is part of a new genre</p>	<p>The text has been amended. Please see the Table, answer 8.</p> <p>The text has been amended.</p> <p>The text has been changed.</p>

called pod-mods. It is like first-generation devices in that it does not afford control over power levels or customization of device components; users only choose among the available flavoured liquids. What sets them apart is the relatively small size and specific design with a striking resemblance to USB flash drives.”Strongin, 2019: “The brand with the largest e-cigarette US market share (~50% as of 2017 and growing) is JUUL. JUUL e-cigarettes are notable for their popularity among teens. These devices do not fall into any of the four generation classifications, but rather are part of a new genre called pod-mods. JUULs are like first generation devices in that they do not afford control over power levels or customization of device components; users only choose among the available flavored liquids. What sets JUULs apart is their relatively small size and sleek, striking resemblance to USB flash drives.”Reports from both the PHE and NASEM provide a more detailed description of e-cigarette device and e-liquid characteristics that the SCHEER opinion could refer to. Furthermore, some technical issues with this section require revision. Pg 20, ln 50: “These early systems were generally inefficient at delivering nicotine, in part because the particle sizes of the aerosol were too large to penetrate deep into the lungs” (Glantz et al., 2018).”The veracity of this statement is questioned, particularly since the authors of the original report did not provide a reference.” As most nicotine is deposited in the lung in the vapor phase, particle size of e-liquid aerosol has negligible effects on lung penetration as noted in the 2018 NASEM report.

Quoted studies were uploaded with this submission in full (as .pdf) or as a first page .jpg file –for reference purposes-where a full upload was not possible because of the 1MB file size upload limitation or because of copyright rules.

Ref:

Talih S, Salman R, El-Hage R, et al Characteristics and toxicant emissions of JUUL electronic cigarettes Tobacco Control 2019;28:678-680.

National Academies of Sciences, Engineering, and Medicine. 2018. Public Health Consequences of E-Cigarettes. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24952>.

Strongin (2019). Annu Rev Anal Chem 2019 Jun 12;12(1):23-39. doi: 10.1146/annurev-anchem-061318-115329.

Thank you for the comment.

The text of the opinion is amended to underline the review paper Tomasz R. Sosnowski and Marcin Odziomek (2018) devoted to investigation of the dynamics of the particles and the role of their size.

The paper has been on the list of references.

17	Woessner Julie, Intern	6.2. Design Features	Page 21	/	Lines 25-36
The SCHEER seems to focus on a particular US brand of pod					

	<p>ational Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU</p>	<p>systems (we note that the phrase “pod-mods” is not widely used, and the phrase “pod systems” is more commonly used). However, there are many different pods systems on the EU market, most of them refillable. The EU-CEG data containing the characteristics of any vaping products on the EU market should have been used in this section rather than the “description” of a single product with an emphasis on the popularity of this product in a single population category on another continent. Small pod systems are part of a natural evolution in vaping devices, now that the technology allows smaller devices that satisfy nicotine users' needs (as opposed to the first generation devices, which were small, but not as satisfying). It has to be noted that a study found no difference, except nicotine concentrations, between the US version and the UK version of the product emphasised here. See Talih et al., A comparison of the electrical characteristics, liquid composition, and toxicant emissions of JUUL USA and JUUL UK e-cigarettes, 2020 (uploaded).</p> <p>Page 21 / Line 33 The SCHEER should define what is a typical USB flash drive form factor.</p> <p>Page 21 / Lines 43-45 While this no doubt creates more work for scientists, the diversity in products (devices, flavours, and nicotine strength) is what allows nicotine users to easily find a product combination that allows them to quit smoking. Ref: Talih (2020). A comparison of the electrical characteristics, liquid composition, and toxicant emissions of JUUL USA and JUUL UK e-cigarettes. https://doi.org/10.1038/s41598-020-64414-5</p>	<p>US data may not necessarily reflect the exact situation in the EU, but trends coming from the US frequently also impact European markets. See table 1, answer 8. No changes in the text are necessary.</p> <p>In the Opinion the SCHEER acknowledged that there are different types of e-cigarettes in section 6.3. However, the SCHEER does not discuss the particular brands in the Opinion.</p> <p>Page 21 / Line 33: This a technical question which is out of the scope of this Opinion.</p> <p>Page 21 / Lines 43-45: This a hypothesis of the commentor. Please see Table 1, answers no 1, 6 and 7.</p>
<p>18</p>	<p>No agreement to disclose personal data</p> <p>6.2. Design Features</p>	<p>p. 21, l25: All American market’s data and references, in particular those relating to nicotine concentration and consumer preferences, are not relevant with regard to the European market due to cultural and regulatory differences.</p> <p>p. 21, l43: It should be pointed out that the crisis occurred in the U.S. (EVALI) was due to the marketing of products contained in</p>	<p>US data may not necessarily reflect the exact situation in the EU, but trends coming from the US frequently also impact European markets.</p> <p>Please see Table 1, answer 8. The text was revised – no mentioning of crisis</p>

			"closed systems". Personal liquids mixing operations have nothing to do with what has happened.	
19	Ollila Eeva, Canc er Society of Finland, Finland	6.3 European Regulatory Framework	<p>The high number of notifications on attempts to put products on the market limits seriously the member states' ability to keep updated which products have entered the market, to ensure that information on the notifications is accurate and sufficient, as well as to ensure that products that have entered the market are safe (Ollila 2019). Based on the SCHEER preliminary opinion the following conclusions can be drawn:</p> <ol style="list-style-type: none"> 1. The safety of e-cigarettes is not yet well known, especially concerning the flavours, possible metals and ultrasmall particles. This is further complicated by the emerge of new types of devices and increased power. A precautionary approach, especially as regards adolescents' health should be taken. 2. E-cigarettes appeal strongly to adolescents, and youth appealing flavours play a significant role in that appeal. Serious considerations on EU-level measures to improve protection of youth from e-cigarettes should be considered. These considerations should include stricter regulation on youth appealing flavours, including considering banning flavours other than that of tobacco, as well as forbidding advertising, including in social media, and implementing display ban. 3. The regulation of device types and power should also be considered at EU level. 4. As e-cigarettes are often used together with conventional tobacco products, the health effects of concomitant use deserve more attention in the final SCHEER opinion. 5. The existing notification scheme without resources to study the notification information, and even more so the accuracy of the information of the products intended for the market, do not ensure the safety of the e-cigarettes in the market. EU level measures to ensure safety should considered. <p>Ref: Ollila (2019) See you in court: obstacles to enforcing the ban on electronic cigarette flavours and marketing in Finland</p>	<p>Aspects of risk management have been not addressed by the SCHEER.</p> <p>Aspects on dual users have been added in the final Opinion.</p>
20	Cox Sharon ,University College London	6.3 European Regulatory Framework	<p>Sentences 45-47.</p> <p>The report states that "many e-cigarette users also mix their e-liquid themselves". This is cited without reference and without data. This statement is inaccurate and misleading for several reasons. The first, is that as stated in the report, the vast majority of sales of</p>	<p>The final Opinion has been revised: E-liquids are commercially available and manufactured, however some users of e-cigarettes prefer to prepare them at home (Cox 2019).</p>

,United Kingdom

e-liquids are factory made ready mixed nicotine containing flavoured e-liquids. If this is not the case and the report is referring to flavour shots without nicotine this needs to be stated as this is an important omission. Furthermore, since the full EU TPD implementation of the upper nicotine limit in May 2017, this made purchasing the high strength nicotine solution (70mg/mL) unavailable to vapers. This nicotine strength was used by those who mixed their own to create their own flavoured lower strength e-liquid (see our study Cox et al., 2019). Since this has been banned this has made the practice of DIY home mixing almost impossible. At the current time, if vapers are mixing their own, they are mixing EU regulated and shop bought flavour solutions which are mixed with EU regulated nicotine shots. There is no evidence these flavour-nicotine shot combos are any less safe than other shop bought e-liquid. Due to the foul taste it creates, vapers cannot add very high numbers of nicotine shots to these liquids. Nonetheless, again, this is not a mainstream practice and the word 'many' is misleading.

We published one paper on DIY home-mixing focusing on this practice before the EU TPD ban on higher strength nicotine. We showed that 1) mixing enabled people to enjoy their vaping, 2) flavour combos helped people feel satisfied with vaping and made the taste of smoking aversive, and in the lab quality analysis, 3) the quality of the ingredients in the home mixed liquid was not significantly different to shop bought, 4) the majority of home mixers made nicotine e-liquids below the EU TPD upper limit <20mg/mL.

Ref: Cox (2019) An exploration into "do-it-yourself"(DIY) e-liquid mixing: Users' motivations,practicesand product laboratory analysis

21	Ross Louise,National Centre for Smoking Cessation and Training,United Kingdom	6.3 European Regulatory Framework	Design features (no text box available) 45-47 It is simply not true that 'many' users mix their own e-liquids themselves. In my clinical experience in Stop Smoking Services, not a single person was found who did this. They were scrupulous about buying from reputable sources. Where did you get this incorrect opinion from?
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Please see the reply to comment 20.

22 No agreement to disclose personal data 6.3 European Regulatory Framework page 21, lines: 51-53 This is outside of the scope of this Opinion.

As indicated above, the TPD provides a strong regulatory framework, which has been recently tested during EVOLI crisis. Unlike in the US, there was no outbreak of EVOLI cases in the EU member states. From the perspective of the association of producers, importers and retailers, we appreciate the EU common entry gate system, which we see as both user friendly and effective in ensuring a high level of public health protection.

23 Olteanu Vlad, Juul Labs Inc., Belgium 6.3 European Regulatory Framework Page 23, Line 11 –21: The Tobacco Products Directive provides a regulatory framework that allows for e-cigarettes to be placed on the market, while ensuring a high level of health protection for the public. Provisions that undermine the ability of e-cigarettes to compete with combustible cigarettes, however, keep cigarettes in pole position as the market leader in nicotine delivery. By disadvantaging new, potentially less harmful products like e-cigarettes, these provisions only serve to maintain Europe’s smoking rate at its current high level. Requirements that discourage or delay the development and uptake of competitive alternatives to smoking are likely in effect to sustain tobacco smoking and perpetuate harm to smokers and wider society as a result. To compete with cigarettes, e-cigarettes must be able to deliver nicotine in a sufficiently satisfying manner. The current maximum allowable concentration of nicotine in e-cigarettes in the EU is (20mg/mL), which Line 13 says “allows for delivery of nicotine that is considered to be comparable to the permitted dose of nicotine derived from a standard cigarette during the time needed to smoke such a cigarette.” This statement is false. This 20mg/mL limit was justified on the basis of papers by Prof Farsalinos, who subsequently wrote to the Commission stating that they have misinterpreted his findings. His research instead shows that 20 mg/mL e-liquid provides less than one-third of the nicotine delivered by one tobacco cigarette (Farsalinos 2014) and that 50mg/ml is needed to roughly match a tobacco cigarette. A study by Hajek et al., 2017 compared e-cigarettes with nicotine concentrations ranging from 16mg/mL to 48mg/mL to a conventional cigarette and showed that in each case, the e-cigarette delivered less nicotine than the combustible cigarette. This means

Please see the Table 1, answer No 1.

Please see also Table 1, answer No 9. The Opinion has been amended.

that 20mg/mL e-cigarettes do not provide an experience that approximates that of a cigarette. An experience approximating a cigarette use is necessary for heavy smokers. Higher nicotine content liquids are used by the most dependent smokers, who have the highest risk of smoking-related death and disease and who benefit most from switching to electronic cigarettes. Most dependent smokers need more than 20mg/ml to switch from smoking to vaping. The current limit may also incentivise the sale of e-cigarette devices that operate at higher temperatures, which deliver more aerosol and thus more nicotine per puff from a lower concentration liquid, but has the potential to also result in the increased formation of potentially harmful by-products (Smets et al., 2019). Quoted studies were uploaded with this submission in full (as .pdf) or as a first page .jpg file –for reference purposes– where a full upload was not possible because of the 1MB file size upload limitation or because of copyright rules.

Ref:

Smets et al (2019). When Less is More: Vaping Low-Nicotine vs. High-Nicotine E-Liquid is Compensated by Increased Wattage and Higher Liquid Consumption. *Int. J. Environ. Res. Public Health* 2019, 16, 723; doi:10.3390/ijerph16050723

Hajek et al (2017). Nicotine delivery to users from cigarettes and from different types of e-cigarettes. *Psychopharmacology* (2017) 234:773–779 DOI 10.1007/s00213-016-4512-6

Farsalinos et al (2014). Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *SCIENTIFIC REPORTS*. 4 :4133 DOI:10.1038/srep04133

Farsalinos (2014). The European Commission has misinterpreted my scientific research on nicotine in e-cigarettes. <http://www.ecigarette-research.org/research/index.php/whats-new/whatsnew-2014/147-misinterpreted-research?tmpl=component&print=1&page>

WHO (2019). European Tobacco Use. Trends Report 2019.

24 Vuerich Michela, A NEC, European consumer voice in standardisation, Belgium

6.3 European Regulatory Framework

Page 22, lines 1-33: It remains to be seen whether the notification requirements of the TPD will be of great help in the assessment of the safety of e-cigarettes. The requirements suffer from a number of shortcomings such as a lack of specific data requirements, e.g. the kind of toxicity data (e.g. inhalation studies in accordance with OECD guidelines), harmonised test protocols for emission measurements etc.) in absence of a clearly defined risk assessment procedure. The required CLP data are of limited use as they could be found also without a notification requirement once the ingredients are known. In addition, they are limited to substances with harmonised classification and do not include classifications

Here the current requirements of the TPD are summarised. The SCHEER agrees that the amount of data is big and the SCHEER takes a pragmatic approach.

following industry self-assessment. We have already pointed to the example of diacetyl – a substance for which no harmonised classifications exist but classifications have been notified by industry. It is questionable whether the submitted data will match the data needs for the envisaged reasonable risk assessment. We fear that the sheer amount of data will make a systematic evaluation a mission impossible anyway. Therefore we need a more pragmatic approach (as ANEC endeavoured to accomplish).

Page 23, lines 3-4: The TPD provides that only ingredients shall be used in the nicotine-containing liquid that do not pose a risk to human health in heated or unheated form. However, in absence of a generally accepted risk assessment methodology these provisions are just empty words. We should verify on the basis of which criteria whether the requirements are met? We believe that SCHEER should address this point!

Page 23, lines 23-25: We have already pointed out that the TPD does not specify the requirements and test methods for determining whether e-cigarettes and containers for e-liquids are child resistant. Hence, conformity with the TPD provision cannot be verified.

25	Vuerich Michela,A NEC, Belgium	6.3 European Regulatory Framework	6.3 European Regulatory Framework	<p>Page 22, lines 1-33: It remains to be seen whether the notification requirements of the TPD will be of great help in the assessment of the safety of e-cigarettes. The requirements suffer from a number of shortcomings such as a lack of specific data requirements, e.g. the kind of toxicity data (e.g. from inhalation studies), harmonised test protocols for emission measurements etc.) in absence of a clearly defined risk assessment procedure. The required CLP data are of limited use as they could be found also without a notification requirement once the ingredients are known. In addition, they are limited to substances with harmonised classification and do not include classifications following industry self-assessment. For instance, diacetyl (butane-2,3-dione) does not have any harmonised classification and is nevertheless known as substance of concern when heated and inhaled (bronchiolitis obliterans). Diacetyl was notified Acute Tox. 3 with H331 (toxic if inhaled) by almost all notifiers. It is questionable whether the submitted data will match</p>
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Please see the response to comment 24.

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26 Vuerich Michela,A NEC, European Consumer voice in standardisation,Belgium

6.3 European Regulatory Framework

Page 22, lines 1-33: It remains to be seen whether the notification requirements of the TPD will be of great help in the assessment of the safety of e-cigarettes. The requirements suffer from a number of shortcomings such as a lack of specific data requirements, e.g. the kind of toxicity data (e.g. from inhalation studies), harmonised test protocols for emission measurements etc.) in absence of a clearly defined risk assessment procedure. The required CLP data are of limited use as they could be found also without a notification requirement once the ingredients are known. In addition, they are limited to substances with harmonised classification and do not include classifications following industry self-assessment. For instance, diacetyl (butane-2,3-dione) does not have any harmonised classification and is nevertheless known as substance of concern when heated and inhaled (bronchiolitis obliterans). Diacetyl was notified Acute Tox. 3 with H331 (toxic if inhaled) by almost all notifiers. It is questionable whether the submitted data will match the data needs for the envisaged reasonable risk assessment. We fear that the sheer amount of data will make a systematic evaluation a mission impossible anyway. Therefore we need a more pragmatic approach (as ANEC endeavoured to accomplish).

Please see response to comment 24.

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27	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.3 European Regulatory Framework	Page 21 / Lines 51-52	Please see Table 1, answer 8.
			Page 22 / Lines 15-16	
			Page 23 / Lines 12-14	

Considering that this Opinion relies massively on US data and “trends”, the SCHEER should clearly state here that there is no such high-level health protection regulation as the TPD in the US covering vaping products. It should be clearly stated throughout the whole Opinion each time US data are used to assess a risk.

The SCHEER states that the EU-CEG data “may have significant utility in future product risk assessments”. The EU-CEG reporting system has been in place since 2014 and yet, to the best of our knowledge, there has been no serious attempt to utilize the data to assess risks. We question why this has not been done despite the “big body of data submitted by manufacturers”? Specifically, we question why SCHEER has not used this European-wide information base for this risk assessment Opinion.

The SCHEER should clearly emphasise the protection provided by TPD Art. 20.3(d) that “only ingredients of high purity are used in the manufacture of the nicotine-containing liquid”, which applies not only to the non-nicotine-containing ingredients, but to the nicotine itself. See our comment on nicotine in the TERMINOLOGY section.

Please see the Table 1, answer Nr 1. It has to noted, that products from the US market do not fall under the European TPD and the safety levels herein. information from EU-CEG available to the SCHEER was used within this Opinion.

This paragraph gives a brief summary of TPD.

			The sentence “This concentration allows for a delivery of nicotine that is considered to be comparable to the permitted dose of nicotine derived from a standard cigarette during the time needed to smoke such a cigarette” is simply wrong. Page 33 lines 14-17 the SCHEER itself wrote: “research showed that there is little relationship between nicotine concentration in e-liquids and nicotine concentration in the resulting aerosol, because the composition of the aerosol also depends on the characteristics of the electronic cigarette (temperature, coil,power, ventilation (Goniewicz, et al., 2014; Peace, et al., 2016)”	This sentence has been removed. Please see the Table 1, answer Nr 9.
28	Brose Leonie, King's College London, United Kingdom	6.3 European Regulatory Framework	European Regulatory Framework, Page 21, line 51-57, page 22, line 1-28, page 23, lines 3-25. The terms of reference include helping the Commission in assessing the potential need for legislative amendments’ however the preliminary Opinion does not appear to include the few studies that have evaluated of the effect of the implementation of the Tobacco and Related Products Regulations (2016). For example, Lee et al (2019) investigated 1) awareness of the new regulations among the sample of 1,606 smokers, ex-smokers and vapers several months after implementation of new regulation; 2) product use among vapers before and after implementation (sample size between 199 and 388); 3) association between use of compliant tank sizes, nicotine strength and refill volumes before implementation and smoking after full implementation of the regulation among 480 vapers (regardless of their smoking status in 2016). Awareness of regulations overall was low and higher among vapers; it was highest for restrictions to the refill volume (10.1%; 37.4% among vapers) and nicotine concentration (9.5%; 27.3% among vapers). Higher proportions in 2017 than in 2016 used TPD-compliant refill volumes (60.0% to 73.7%, $c2(1)=10.9$, $p=0.001$) and nicotine concentrations (89.2% to 93.9%, $c2(1)=7.41$, $p=0.007$), with little change for cartridge/tank volume (77.1% to 75.5%, $c2(1)=0.38$, $p=0.540$). Use of compliant products in 2016 was not associated with smoking in 2017. The likelihood of smoking was similar for those using no or one TPD compliant product (tank size, nicotine strength, refill volume) as it was for those using two (OR=1.10; 95% CI: 0.47-2.59) or three (OR 1.56, 95% CI: 0.69-3.55). Lee (2019) and McNeill et al (2019)	This is outside of the scope of this Opinion.

			recommended that an evaluation of the impact of regulation on smoking and vaping behaviours are needed.	
29	No agreement to disclose personal data	6.3 European Regulatory Framework	p.21, 151: In terms of definitions, Directive 2014/40/EU aims at regulating electronic cigarettes, regardless of their nicotine content; as a matter of fact, Italian relevant Authorities (health, tax, customs, etc.) have always considered electronic cigarettes as products that fall under the scope of TPD, whether with nicotine content or not.	In the TPD, the e-cigarettes without nicotine are not regulated but the national legislation can differ.
30	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	6.3 European Regulatory Framework	Page 21, lines: 51-53 Current European regulatory framework (Tobacco Products Directive 2014/40/EU) is comprehensive and sufficient. In general, e-cigarettes and other less risky alternatives should have a different regulatory framework that is applied for cigarettes. Subjecting e-cigarettes and other smoke-free products to the same restrictions as for combustible cigarettes can have unintended consequences. For example, such strict regulation could discourage smokers from using a less risky products.	This is up to policy makers (risk management).
31	Ward Emma, University of East Anglia, United Kingdom	6.3 European Regulatory Framework	Lines 3-29 This section outlined the TPD regulations which impact the consumer including nicotine strength and bottle volume restrictions. Our recently published work, "A Qualitative Exploration of Consumers' Perceived Impacts, Behavioural Reactions, and Future Reflections of the EU Tobacco Products Directive (2017) as Applied to Electronic Cigarettes", 2020, Tobacco Use Insights, 13, (doi.org/10.1177/1179173X20925458), is relevant to this section as it explored the consumer experience of the TPD legislation. As part of a wider study into e-cigarette user trajectories (E-Cigarette Trajectories, funded by Cancer Research UK) qualitative data, collected between March 2018 and March 2019, relating to participant views of the TPD were extracted from 160 interviews/extended surveys of e-cigarette consumers and analysed thematically. We found that awareness of the TPD among consumers was not universal. Participants' smoking behaviour did not appear to be influenced by the legislation. Participants were reassured by manufacturing regulations and requirements for ingredients labels and wanted further regulation around product ingredients. Participants responded negatively to changes perceived to cause inconvenience (e.g. smaller tanks) and extra plastic waste	The comment is beyond the scope of the Opinion.

			(e.g. small 10ml bottles). The product restrictions (such as tank size and nicotine strength limits) prompted some participants to purchase non-compliant products illegally from other non-EU countries and the black market, potentially putting their safety at risk. Our analysis indicated that, from a consumer perspective, e-cigarette regulation should focus on ensuring product safety, especially regarding e-liquid ingredients. Raising awareness of the TPD among consumers and smokers could be beneficial as some consumers perceived electronic cigarettes to be unregulated.	
32	Ollila Eeva, Cancer Society of Finland, Finland	6.4 Chemical ingredients in e-liquids	The study notes the high number of e-cigarette linked notifications that each member state receives (Table 1). As is mentioned (p 24) based on the study in the Netherlands by Havermans et al 2019, the number of marketed e-liquids can be extremely high in individual member state. Furthermore, the composition of the e-liquids have been shown to differ from the list of ingredients in the labels (Han et al 2014, DOI: https://doi.org/10.1186/s12971-014-0023-6).	Thank you for this comment.
33	Lazzarotti Alessandro, Zio Svapodi Alessandro Lazzarotti, Italy	6.4 Chemical ingredients in e-liquids	<p>Vietare gli aromi nei liquidi è da fascismo puro, non siamo al servizio delle lobby del tabacco e soprattutto non siamo tabacco, quindi sono a favore degli aromi nei e-liquid</p> <p>ABSTRACT Page 2 lines 13-14 “The overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” Nicotine produces minor cardiovascular events but not major ones. CV risk in smoking comes from CO, not nicotine. “Snus delivers a high dose of nicotine with possible hemodynamic effects, but its impact on cardiovascular morbidity and mortality is uncertain.” And “toxic components other than nicotine appear implicated in the pathophysiology of smoking related ischemic heart disease.” Nicotine concentrations in NRT users’ plasma comparable to those using ecigarettes, and: “The use of NRT is not associated with any increase in the risk of myocardial infarction, stroke, or death.” “While people with established CVD might incur some increased risk from ecigarette use, the risk is certainly much less than that of smoking. If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be substantially reduced and there would likely be a substantial net benefit for cardiovascular health.</p> <p>ABSTRACT Page 2 lines 42-44 Regarding the role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people, the SCHEER concludes that there is strong evidence that electronic cigarettes are a gateway to smoking for young people SCHEER cites papers showing smoking and vaping association & interprets the link as causal. “Gateway” is impossible to determine:</p>	The Opinion has been revised accordingly.
				Please see table 1, answer 5.

“We strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field.”

“If a true gateway effect were to exist, it would probably have little effect on smoking prevalence. No available evidence exists that increasing e-cigarette use has slowed the decline in smoking prevalence; indeed, the decline appears to have accelerated.” Lee

“There is a longitudinal association between adolescent vaping and smoking initiation; however, the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders.”

ABSTRACT Page 2, lines 49-52

“Regarding the role of electronic cigarettes in cessation of traditional tobacco smoking, the SCHEER concludes that there is weak evidence for the support of electronic cigarettes effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate.”

Brand new Cochrane review "There is moderate certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT."

"More people probably stop smoking for at least six months using nicotine e cigarettes than using nicotine replacement therapy (3 studies; 1498 people), or nicotine free e-cigarettes (3 studies; 802 people). We are uncertain if there is a difference between how many unwanted effects occur using nicotine e cigarettes compared with using nicotine free e cigarettes, nicotine replacement therapy, no support or behavioural support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for all groups."

“The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group” Hajek

“Use of e cigarettes and varenicline are associated with higher abstinence rates following a quit attempt in England.”

“After 6 months about 20% of the entire sample stopped smoking. Participants who used e-cigarettes with nicotine smoked fewer tobacco cigarettes than any other group after 6 months (p < .020). Our data add to the efficacy and safety of ecigarettes in helping smokers reduce tobacco consumption and improving pulmonary health status.”

“99% of those surveyed smoked before vaping. 81% agreed they could quit smoking with vaping, compared to traditional cessation aids. 84% experienced improvements in health.”

“The number of daily ex-smokers who have quit smoking for more than six months and who believe that vaping has helped them quit smoking is estimated at around 700,000 since the arrival of the e-cigarette on the market in France”

2019 Irish data shows a drop in smoking prevalence from 23% in 2015 to 17% in 2019. Daily vaping rose by 3-5% in the same period.

SUMMARY Page 8 lines 13-15

It is also interesting to note that a modified version of a popular pod device with a 76% US-market share is now on the EU market (a reference to Juul) 76% is not accurate - taken from Nielsen data from petrol stations & convenience stores only - does not include vape store and online sales

Please see table 1, answer 6.

This has been replaced throughout the report by a ‘large market share’.

Very recent ASH UK factsheet found that: “The most popular products for all vapers are still tank systems, with 77% of vapers reporting using them. In 2020, 19% of vapers reported using cartridge/pod systems, similar to 2019 levels. When asked what brands they use, for those who have tried vaping and use cartridges, the two most popular type of systems remain, Vype (20%) and Blu (17%), but Juul is now used by the same proportion of users as Logic (10%). Juul was new on the market in 2018.”

SUMMARY Page 8 lines 22 - 23

“Some data available from the US indicate that the prevalence of electronic cigarette use is increasing in children and adolescents.”

Most recent data US data actually shows a further 29% decrease in youth use: “In 2020, approximately one in five high school students and one in 20 middle school students currently used e-cigarettes. By comparison, in 2019, 27.5% of high school students (4.11 million) and 10.5% of middle school students (1.24 million) reported current e-cigarette use.”

SCIENTIFIC OPINION

page 10, lines 7-9

“The assessment should include and address the role of e-cigarettes, looking into potential impacts on the EU context

SCHEER has not followed their own terms of reference

Have relied on US studies

Have not considered EU studies, for example: Chyderiotis, DKFZ, Gorini, Brożek

SCIENTIFIC OPINION

Page 15 lines 19-24 The overall weight of evidence for risk for carcinogenicity of the respiratory tract due to longterm, cumulative exposure to nitrosamines and due to exposure to acetaldehyde and formaldehyde is weak to moderate.

Public Health England calculated the cancer potency of vaping to under 0.5% that of smoking.

Stephens et al (2018) found that e-cigarette users were typically exposed to 0.4% of the lifetime cancer risk of smokers.

RATIONALE

Page 20 lines 26-27 This Opinion is restricted to the terms of references given by the European Commission. It covers electronic cigarette products complying with the TPD

Opinion relies on US studies, which do not involve TPD compliant products.

6.5.3 Hazard identification of most relevant compounds Page 40 lines 10-11

“About 60 mg is fatal for humans. Death from respiratory paralysis occurs after only a few minutes.”

“Nicotine is a toxic compound that should be handled with care, but the frequent warnings of potential fatalities caused by ingestion of small amounts of tobacco products or diluted nicotine-containing solutions are unjustified and need to be revised in light of overwhelming data indicating that more than 0.5 g of oral nicotine is required to kill an adult.”

Please see table 1, answer. 8.

See Table 1, answers 2 and 8.

Please see Table 1 answer 8

See Table 1, answer 1.

See replies to comment 112 and 193.

“There is a mismatch between the generally accepted lethal oral nicotine dose of 60 mg, resulting in approximately 180 µg L-1 plasma concentration, and the 4.4- to 8.9fold higher lethal plasma concentrations we found in cases of e-liquid intoxication.”

6.5.3 Hazard identification of most relevant compounds

Page 41 lines 34 - 57

“Besides possible toxic effects...difficult to quit...”

“Attractiveness” & efficient nicotine delivery are crucial for e-cigarettes to win smokers over from smoking. Age of sale restrictions can deter youth access while allowing vaping to benefit adults.

Farsalinos: “Due to the fact that adoption of ECs by youngsters is currently minimal, it seems that implementing regulatory restrictions to flavours could cause harm to current vapers while no public health benefits would be observed in youngsters.”

6.5.4 Human evidence for health impacts of electronic cigarettes

Page 46 line 18 - page 55 line 13

Numerous relevant studies omitted. No comparison with smoking. No discussion of health benefits from switching from smoking to vaping. Need to frame according to risk

6.5.4 Human evidence for health impacts of electronic cigarettes Page 47 Lines 12-16

“Acute effects If assessed, acute mouth / throat irritation, and cough are reported by a sub-group of users (Polosa et al., 2011; Palamidis et al., 2017), these effects are not attributed to the nicotine content (Palamidas et al., 2017). It is speculated that these effects are caused by hyperventilation, which is associated with long puffing time (Morjaria et al., 2011)”

Minor throat irritation & coughs are short term minor effects when switching

Hajek RCT on e-cigarettes vs NRT reported: “65.3% of e-cig users 51.2% of NRT users experienced this minor irritation. However, the e-cig group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group”. “The switch from smoking to vaping was associated with a reduced incidence of self-reported respiratory infections.”

6.5.4 Human evidence for health impacts of electronic cigarettes Page 49 line 2

Short-term use of an electronic cigarette has acute effects on airways physiology and 3 respiratory symptoms in COPD smokers,

Just published 5 year follow up of COPD smokers found: “The present study confirms our previous research that switching from smoking to vaping ameliorates respiratory health in COPD patients and that these positive health effects may persist long term.35,36 - Polosa 5 year follow up” And: “A major finding of the study is that COPD exacerbations were reduced by approximately 50% in patients who stopped or considerably reduced their smoking consumption after switching to vaping.” Consistent with findings from same cohort at 24 months and 36 months.

6.5.4 Human evidence for health impacts of electronic cigarettes

Page 53 lines 30-32

See table 1 answer No 1.

Please see table 1 answer 1

Indirect electronic cigarette explosion injuries occur as a consequence of fire when the device ignites and causes a house or car fire, causing subsequent flame burn injuries and inhalation injuries.

No comparison with fires caused by combustible cigarettes

US NFA 18,000 fires annually in US caused by smoking materials, 2012 - 2016

PHE 2018 review: "Between 2015 and 2017 there were 44 smoking-related deaths due to fires, and no EC-related deaths due to fires, and 13 fires due to ECs and 3,527 related to cigarettes

6.6 Role in the initiation of smoking (particularly focusing on young people)

Pages 62-70

SCHEER acknowledges most studies they include are from USA However, key differences between USA & Europe - regulatory differences - product availability USA youth usage includes high nicotine pods & cannabis products - Past 30 day use main driver in USA, not regular use - SCHEER does not consider US youth smoking rates, which have fallen since ecigarettes were introduced

Jarvis: "While experimental use of e-cigs increased in the USA, frequent use and signs of ecigarette dependence remained rare in students who had only ever used ecigarettes and never any other tobacco product."

Some key EU studies which were not included:

German Cancer Research Centre report DKFZ

little evidence for gateway effect: "Auch wenn zahlreiche Studien einen Zusammenhang zwischen EZigarettenkonsum und Rauchen nahelegen, wirkt sich dies auf Bevölkerungsebene bislang offenbar nur wenig und unterschiedlich Aus" Google translate: "Even if numerous studies suggest a connection between e-cigarette consumption

Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? (Jarvis et al., 2020)

DKFZ 2020. E-Zigaretten und Tabakerhitzer – ein Überblick

and smoking, this has apparently only had little and different effects at the population level"

Chyderiotis et al, France - "Among ever-smokers, adolescents who declared having ever used e-cigarettes were less likely than those who did not to transition to daily smoking at 17."

Gorini, Italy: "Adolescents who currently smoked tobacco cigarettes and/or used electronic cigarettes non- significantly increased from 21% in 2010 to 28% in 2018, and a 3fold significant increase of exclusive electronic cigarette users were recorded in Italy. Moreover, even though smoking prevalence stalled from 2010 to 2018, significant but little decreases in smoking prevalence from 23% in 2014 to 20% in 2018, and from 18% to 10% among exclusive tobacco cigarette smokers, and a significant increase from 6% to 9% among dual users were recorded."

Brożek Survey of university students in Belarus, Lithuania, Poland, Russia, and Slovakia. Overall current smoking status: 12.3% cigarette smokers, 1.1% e-cigarette users, 1.8% dual users, the rest non smokers.

The Scheer is very clear and precise '...For both poisoning and injuries due to burns and explosion, the evidence for the intrinsic capability to cause health problems is strong, but the incidence is quite low: only few case reports are available'

Two issues are clearly stated:

- It is noted that burns and explosions are a realistic health concern there is clear evidence from studies
 - The incidence is quite low meaning that the frequency is very low
- The mandate of the Opinion is not to compare with other types of electronic devices and/or other types of cigarettes.

See table 1 answer No 8.

See table 1 answer No 2.

“Young adults who used e-cigarettes daily in 2016–18 were less likely to smoke daily and more likely to have recently quit smoking compared to non-daily, former or never users.”

Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? (Chyderiotis et al., 2020)

Prevalence of tobacco smoking and electronic cigarette use among adolescents in Italy: Global Youth Tobacco Surveys (GYTS), 2010, 2014, 2018 (Gorini et al., 2020)
The Prevalence of Cigarette and E-cigarette Smoking Among Students in Central and Eastern Europe— Results of the YUPESS Study (Brożek et al., 2019)

6.6 Role in the initiation of smoking (particularly focusing on young people)

64 line 34 - 66 line 2

European Heart Network recommends flavours should be prohibited (line 55)

Royal College of Physicians: “However, if [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumerfriendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.” From section 12.10 page 187

Bans lead to more smoking: “local bans can still significantly reduce overall e-cigarette use and cigar smoking but may increase cigarette smoking.”

SCHEER disregards benefits to adults - Importance of flavours to adults shown in many studies, including Havermans study (frequently quoted in SCHEER):

“Furthermore, adults who completely substituted the use of conventional cigarettes by e-cigarettes have often initiated e-cigarette use with fruity flavours rather than tobacco flavours, or switched from tobacco to nontobacco e-liquid flavours over time”

Please see table 1, answers 1 and 7.

34 No agreement to disclose personal data 6.4 Chemical ingredients in e-liquids

Page 24 Line 1: Table 2 lists ingredients with Classification Labelling and Packaging (CLP) hazard codes. These apply to the neat compounds and do not take dosage into account. E.g. Ethanol H225 is highly flammable, but not within the doses typically used in an e-liquid. This important qualification is missing, raising doubt amongst consumers and regulators on the safety profile of e-liquids. Whilst e-cigarette and their e-liquids are not risk free, the available scientific evidence indicates e-cigarettes have a substantial reduced risk profile compared to cigarette smoke – a point recently documented[1] by the UK Government’s Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) - but ignored by SCHEER.

The Opinion has been revised.

P25 L13: No responsible manufacturer markets “sandwich”, “buttermilk” or “lavender” products. IMB products are all responsibly marketed with flavour names, descriptors, and

Risk management is outside of the scope of the SCHEER.

packaging designs that do not appeal to youth or non-smokers. We believe any e-cigarette use by youth is unacceptable and we recommend age restrictions at point-of-sale are rigorously enforced, and that marketing, branding, and package labelling clarifies that e-liquids contain nicotine and are intended for use by adult smokers only.

P25 L30: There is an error here: the mean number of flavorings in the error bars are reportedly larger than the number of flavours. There are some basic errors throughout the document that could have been avoided by adequate proof reading and external peer-review of the Opinion.

The errors have been corrected in the Opinion.

P29 L39; There is another error here: '20mm in size' should be 'µm'.

The error has been corrected in the Opinion.

P23 L36: By raising ingredients standards, the EU can guarantee a level playing field amongst e-cigarette manufacturers in addition to boosting consumer trust and safety. IMB encourages regulators and standards bodies to ensure all e-cigarettes in different jurisdictions meet similar high standards with regards to e-liquid ingredients. It is our view that all EU manufacturers selling e-liquids should be held accountable to the same standards, which should apply equally to nicotine and non-nicotine containing e-liquids. IMB believes pod-based e-cigarette devices offer the best opportunity to ensure ingredients fall within pre-defined and regulated standards and we support regulatory measures that limit the ability of users to alter the ingredients used within them.

Risk management is outside of the scope of the SCHEER.

Ref: UK Committee on toxicity of chemicals in food, consumer products and the environment (COT): Statement on the potential toxicological risks from electronic nicotine (and nonnicotine) delivery systems (E(N)NDS – e-cigarettes) <https://cot.food.gov.uk/sites/default/files/202009/COT%20E%28N%29NDS%20statement%202020-04.pdf>

35	aba, test, Luxembourg	6.4 Chemical ingredients in e-liquids	scientific comment	<i>There is no comment included in the contribution.</i>
36	Compernelle Thomas, British	6.4 Chemical ingredients in e-liquids	SCHEER's approach to e-liquid ingredients has limitations, provides inappropriate information and does not advance sound scientific principles, for example Table 2 (P24).	

American
Tobacco,B
elgium

Considering e-liquid (EL) ingredients based on recipe quantity mass (mg) without reflecting product volume does not accurately inform prioritization. EL are available in varying volumes, which could result in dramatically different reporting of final ingredient concentrations (mg/mL). Mass alone does not inform potential for human exposure and should not be considered for prioritization purposes.

No transparent process has been described for identification and selection of the CLP classifications provided in Table 2. Classification of EL ingredients according to minor, self-notified CLP is inappropriate. For example, the 3 propylene glycol (PG) classifications provided only account for 50 (H319 Eye Irrit 2), 12 (H315 Skin Irrit 2), and 21 (H302 Acute Toxicity if Swallowed) self-notifications, while 6420 self-notifications are reported as “not classified”.

CLP information has been removed from table 2.

PG has been evaluated in multiple toxicological studies, including oral and inhalation routes, demonstrating a low potential to manifest toxicity. The EFSA Panel on Food Additives and Nutrient Sources added to Food reaffirmed an ADI of 25 mg/kg bw/day (1). Approvals by regulatory bodies for use in food for human consumption do not include evaluation for potential respiratory toxicity when used as a tobacco product ingredient. Such approvals for use in food do, however, demonstrate that qualified scientists have concluded that PG is of low inherent toxicity. EFSA specifically concluded that acute toxicity was low based on the review of numerous acute toxicity studies, with LD50 values ranging from 18,350-33,500 mg/kg bw across mice, rats, rabbits and guinea pigs (1). These data are not consistent with an H302 CLP classification (harmful if swallowed).

Furthermore, the CLP classifications provided in Table 2 do not align with the hazard identification. For example, the carriers, PG and glycerol are identified as respiratory tract and GIT mucosa irritants (Table 7) with a footnote caveat that “data is scarce” without further explanation regarding weight of evidence.

PG has broad applications in pharmaceutical and consumer

products including skin care, personal hygiene, cosmetic products, and as an inactive ingredient in drug formulations (2). It is a solvent for food colors and flavors and used as a pharmaceutical excipient in several dosage forms, including as a co-solvent in inhaled aerosols (10–25%) (3,4). These diverse approvals for use in foods, cosmetics, personal care products and pharmaceuticals are all consistent with a very low order of toxicity for PG and none are consistent with any expectation that it could manifest any meaningful respiratory toxicity.

In 2018, Dalton et al. assessed the potential human toxicity of acute PG inhalation exposure in 10 men and 10 women exposed for 4 hours at 100 mg/m³ and 30 minutes at 200 mg/m³ to PG aerosols (5). Objective measures evaluated in this study included ocular irritation via eye blink task and eye photography, as well as pulmonary function via spirometry. Subjective measures included health symptoms ratings, irritation and dryness ratings of eyes, nose, throat and mouth. No respiratory or ocular effects were observed, leading the authors to conclude that, at the concentrations tested, PG does not affect respiratory function or produce ocular irritation (5). Overall, these data are not consistent with an H319 CLP classification (Eye Irrit 2) or respiratory irritation hazard for PG.

Given the shortcomings outlined, we respectfully request SCHEER review their conclusions, referring to the attached literature.

Ref:

EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, et al. Scientific Opinion on the re-evaluation of propane-1,2-diol (E 1520) as a food additive. *EFSA Journal*. 2018; 16(4):5235, 40 pp.

Berlin C, McCarver DG, Notterman DA, Ward RM, Weismann DN, Wilson GS, et al. "Inactive" ingredients in pharmaceutical products: update (subject review). *Pediatrics*. 1997; 99(2):268278.

European Medicines Agency. Background review for the excipient propylene glycol in the context of the revision of the guideline on 'Excipients in the label and package leaflet of medicinal products for human use'. Committee for Human Medicinal Products (CHMP). London, UK. CPMP/463/00 Rev. 1; 2014.

37 Olteanu Vlad, Juul Labs Inc., Belgium 6.4 Chemical ingredients in e-liquids

US Food and Drug Administration (FDA). Inactive ingredient search for approved drug products. Rockville, MD.
Dalton P, Soreth B, Maute C, Novaleski C, Banton M. Lack of respiratory and ocular effects following acute propylene glycol exposure in healthy humans. *Inhalation Toxicology*. 2018; 30(3):124-132.

This purpose of section 6.4, “Chemical ingredients in e-liquids” is confusing. The Opinion states on page 23 lines 36-40 that, “The SCHEER considered i) nicotine, ii) carriers (e.g. glycerol and propylene glycol) considered of high importance and present with high frequency at high levels and iii) ingredients present in more than 10% of products tested with a median amount > 1 mg or present in less than 10 % of products tested but with a median amount of > 10 mg (see table 2),” but there is no reference to the application of this consideration in the context of the report. It may be assumed that in considering risk and exposure analysis, these chemicals would be referenced, but that is not explicitly stated and should not be inferred by the reader. Instead 3 of 4 paragraphs in this section are dedicated to discussion of various flavors of ENDS.

Please see reply to comment 34.

No doubt, the wide array of chemicals that may be used in different flavorings have been cause for consideration of modifiable risk factors (see, NASEM report pages 172-181), but this was not discussed here. Simply, the committee referred to a survey of various flavor categories and nicotine concentrations of e-liquids marketed in the Netherlands - and why the committee focused on the Netherlands market was not mentioned (Is the Netherlands market an outlier in the EU market, or is the Netherlands representative of the EU market? This is not known from the text of the Opinion). A description of the type of ENDS or e-liquids (e-liquids for refillable devices, e-liquids for pod-mods, etc) discussed in the Netherlands referenced was not mentioned either making the purpose of this section confusing and out of context with the section description.

As indicated in section 6.4: ‘The Opinion makes use of information from competent authorities in the Netherlands and Greece, which have compiled lists of most common ingredients of e-liquids (see tables in Annex 2).’ Similar information sets are available to all regulators for their respective countries.

A discussion and analysis of chemicals, including flavoring chemicals, found in e-liquids across various ENDS devices could be useful and give context and meaning to this section.
Ref:

SCHEER used relevant data available for its assessment. These data show that the ingredients used in the Netherlands and in Greece are probably representative for the EU market in general.

It is correct that in this Opinion no reference is made to specific e-liquids, since this is not the scope of the Opinion.

The purpose of the section is to give the reader some inside in the large variability of the e-liquids and their composition, but that some chemicals are frequently (in more than 10% of the products), and that some are less frequently used (<10%) but when used having a higher concentration > 10 mg.

National Academies of Sciences, Engineering, and Medicine. 2018. Public Health Consequences of E-Cigarettes. Washington, DC: The National Academies Press. <https://doi.org/10.17226/24952>.

The flavorings are described in section 6.5.2.3 Quantification of aerosol concentrations and in section 6.5.3 Hazard identification of most relevant compounds

38 Ekblad Mikael, Scientific board of the Tobacco-free Finland 2030 organization, Finland

6.4 Chemical ingredients in e-liquids

The SHEER preliminary opinion gives a thorough picture of the state of knowledge concerning the ingredients of e-cigarettes. The study notes the high number of e-cigarette linked notifications that each member state receives (Table 1). As is mentioned (p 24) based on the study in the Netherlands by Havermans et al 2019, the number of marketed e-liquids can be extremely high in individual member state. Furthermore, the composition of the e-liquids have been shown to differ from the list of ingredients in the labels (Han et al 2014). The high number of notifications on attempts to put products on the market limits seriously the member states' ability to keep updated which products have entered the market, to ensure that information on the notifications is accurate and sufficient, as well as to ensure that products that have entered the market are safe (Ollila 2019).

Thank you for the comment. No changes in the Opinion are needed.

It is alarming is that the safety of flavors has in most cases been tested only for per oral use, not when heated and inhaled (see also Stratton et al 2018). It has been earlier postulated that especially sweet flavours would cause irritation and even damage (Ebersole et al. 2020, Iruasa et al. 2020) in mouth and respiratory track (for example Lerner et al 2015).

While it is understandable that it is not possible to give a scientific opinion on the health effects of the ultrasmall particles, as there was no available data, this is also concerning, as it has been postulated that the ultrasmall particles can be especially harmful as they can enter especially deep in the lung tissue and further from there.

Thank you for the comment..

The potential exposure to UFP due to e-cig use is described in some detail on p29 lines 9-47 of the Opinion. Both size/number estimation as well as size/mass estimations are given.

Section weight of evidence: while in general strong to moderate evidence is found concerning the increased exposure to particles due to electronic cigarette us, while nanoparticles are not taken into account due to the scarce data.

It is clear from the attentions given to the nanoparticles in the sections describe above that thte SCHEER considers nanoparticles as potential hazardous but due to the sarce data no weight can be given – and ths no speculations can be made. No change in the Opinion needed.

The SCHEER opinion concludes that flavours are a crucial factor for the adolescents to initiate e-cigarette use. Furthermore, it is noted that adolescents like tobacco flavour less than sweet and other “youth-appealing” flavours, while concurrent or ex-smokers like also tobacco flavour. One must bear in mind that children are more vulnerable to chemical exposures both in physiological and neurological reasons.

Please see table 1, answer 7.

Conclusions

Based on the SCHEER preliminary opinion the following conclusions can be drawn:

1. The safety of e-cigarettes is not yet well known, especially concerning the flavours and the new compounds formed in heating, possible metals and ultrasmall particles, and taking into account the recent developments in the device type and power. No regulation will meet the standards of protecting population the exposure to unknown risks.

Ref: Stratton K, Kwan LY, Eaton DL. Public health consequences of e-cigarettes. A consensus study report of the National academies of sciences, engineering and medicine. USA: The National Academic Press, 2018

Hahn J, Monakhova YB, Hengen J, et al. Electronic cigarettes: overview of chemical composition and exposure estimation. *Tob Induc Dis* 2014;12:23

Ollila E. See you in court. Obstacles to enforcing the ban on electronic cigarette flavours and marketing in Finland. *Tob Control* 2019;0:1-6. doi:10.1136/tobaccocontrol-2019-0055260

Ebersole J, Samburova V, Son Y, Cappelli D, Demopoulos C, Capurro A, Pinto A, Chrzan B, Kingsley K, Howard K, Clark N, Khlystov A. Harmful chemicals emitted from electronic cigarettes and potential deleterious effects in the oral cavity. *Tob Induc Dis*. 2020 May 8;18:41. doi: 10.18332/tid/116988.

Irusa KF, Vence B, Donovan T. Potential oral health effects of e-cigarettes and vaping: A review and case reports. *J Esthet Restor Dent*. 2020 Apr;32(3):260-264. doi: 10.1111/jerd.12583.

Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One* 2015;10:e0166732.

39	Schulz Thomas, German Federal Institute for Risk	6.4 Chemical ingredients in e-liquids	p. 24, table 2 General comments The table gives relevant and new information on the frequency of additives used in E-liquids and on recipe quantities and concentrations. However, the compilation of hazardous properties using hazard statement codes from the CLP regulation (1272/2008/EC) is misleading and inappropriate. It is
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Please see reply to comment 34. The Opinion has been revised.

Assessment, Germany	recommended to remove the column.	<p>Arguments for a removal: The hazard statement codes were developed to label containers of the pure chemical. If mixtures are labelled according to CLP, this has to be performed in compliance with the specific rules of CLP. For example, table 2 mentions ethyl maltol with H302 (Harmful if swallowed). H302 labels acute oral toxicity category 4. The lowest and most powerful LD50 of acute oral toxicity category 4 is 300 mg/kg body weight. According to table 2, the median concentration of ethyl maltol is 0.1%. According to the rules of CLP for mixtures, the content of ethyl maltol in E-liquids does not require a labeling with H302. There are several other compounds in table 2 labeled with H302. Specific rules also apply to mixtures for other hazard statements used in table 2.</p> <p>Furthermore, it is misleading to merge harmonised and self-classification and labelling in one column. Harmonised classification and labelling are legally binding, usually they are the result of a scientific data based evaluation by competent authorities. The European Chemical Agency (ECHA) distinguishes harmonised classifications in the C&L Inventory with light blue color from self-classifications, marked in orange. Self-classification is performed by companies dealing with the chemical and there is no assessment of the scientific basis of the notification at ECHA.</p> <p>Additionally, there are many inconsistencies in self-classification and labelling in table 2. The BfR has evaluated all compounds against the C&L Inventory of ECHA. In table 2 of the report, many hazard statements from the C&L Inventory are presently missing. It is unclear, which criteria have been used for inclusion or exclusion of hazard statements in/from table 2.</p> <p>In conclusion, it is strongly recommended to remove the column.</p>	
40 Schulz Thomas, G erman Federal	6.4 Chemical ingredients in e-liquids	<p>p. 24, table 2 General comments II If it is the decision of SCHEER to retain the column, the following comments should be considered.</p>	Please see reply to comment 34. The Opinion has been revised.

As pointed out above, it is misleading to merge harmonised and self-classification and labelling in one column. It is recommended to use two columns: one with harmonised classification and the other one with self-classification. It is misleading to use only an asterisk for distinction between harmonised and self-classification and labelling.

p. 24, table 2
Specific comments on table 2, if the column on CLP will be retained

1. Mistakes in harmonised classification and labelling, which should be corrected.
Ethyl acetate: table 2 labels H336 with an asterisk for harmonised classification. According to the C&L Inventory of ECHA, the following H-statements are harmonised: H225, H319, H336.
Acetic acid: table 2 labels H314 with an asterisk for harmonised classification. According to the C&L Inventory of ECHA, the following H-statements are harmonised: H226, H314.
Benzyl alcohol: table 2 labels H302 with an asterisk for harmonised classification. According to the C&L Inventory of ECHA, the following H-statements are harmonised: H302, H332.
p. 24, table 2 Specific comments on table 2, if the column on CLP will be retained.

2. Inconsistencies in notified classification and labeling, which should be clarified.
Glycerol: Table 2 states no hazard statements. According to the C&L Inventory of ECHA, the following H-statements have been notified for glycerol: H319 (49 of 5930 notifiers, corresponding to 0.83%), H315 (20 of 5930 notifiers, corresponding to 0.34%), H373 (5 of 5930 notifiers, corresponding to 0.08%), H372 (4 of 5930 notifiers, corresponding to 0.07%) and H335 (2 of 5930 notifiers, corresponding to 0.03%). Is there a reason for exclusion of all hazard statements? Please consider also the evaluation of propylene glycol.
Propylene glycol: Table 2 states H302, H315 and H319. According to the C&L Inventory of ECHA the following H-statements have been notified for propylene glycol: H302 (26 of 6573 notifiers,

corresponding to 0.40%), H315 (12 of 6573 notifiers, corresponding to 0.18%), H319 (58 of 6573 notifiers, corresponding to 0.88%), H335 (7 of 6573 notifiers, corresponding to 0.11%), H317 (2 of 6573 notifiers, corresponding to 0.03%) and H301 (1 of 6573 notifiers, corresponding to 0.02%). In table 2, three hazard statements have been mentioned with notification percentages of 0.18% to 0.88%. Three other hazard statements with notification percentages < 0.012% have been omitted. The comparison with glycerol shows a major inconsistency: Two out of the five hazard statements for glycerol have notification percentages of 0.83% and 0.34%, which corresponds to the values for hazard statements H319 and H302 in propylene glycol. Is there a reason for exclusion in the case of glycerol and inclusion in the case of propylene glycol?

Vanillin: Table 2 states H302, H315 and H319. According to the C&L Inventory of ECHA the following H-statements have been notified for vanillin: H302 (214 of 2395 notifiers, corresponding to 8.94%), H315 (7 of 2395 notifiers, corresponding to 0.29%), H319 (36 of 2395 notifiers, corresponding to 1.50%), H317 (341 of 2395 notifiers, corresponding to 14.24%), H332 (6 of 2395 notifiers, corresponding to 0.25%), H335 (3 of 2395 notifiers, corresponding to 0.13%), and H303 (1 of 2395 notifiers, corresponding to 0.04%). In table 2 three hazard statements have been mentioned with notification percentages of 0.29% to 8.94%. Is there a reason for the omission of H317 with a notification percentage of 14.24%? H317 has been included in table 2 for furaneol.

41	Schulz Thomas, German Federal Institute for Risk Assessment, Germany	6.4 Chemical ingredients in e-liquids	<p>p.24, table 2</p> <p>Specific comments on table 2, if the column on CLP will be retained</p> <p>Ethanol: Table 2 states H225, H319, H350 and H371. According to the C&L Inventory of ECHA, the following H-statements have been notified for ethanol: H225 (13390 of 13396 notifiers, corresponding to 99.96%), H319 (4975 of 13396 notifiers, corresponding to 37.14%), H350 (1332 of 13396 notifiers, corresponding to 9.94%), H371 (665 of 13396 notifiers, corresponding to 4.96%), H302 (668 of 13396 notifiers, corresponding to 4.99%). The C&L Inventory contains 16 more hazard statements for ethanol with notification percentages of < 0.15% each. They were omitted in this comment. In table 2 four</p>	Please see reply to comment 34. The Opinion has been revised.
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hazard statements have been mentioned with notification percentages of 4.96% to 99.96%. Is there a reason for the omission of H302 with a notification percentage of 4.99%?

Maltol: Table 2 states H302 and H319. According to the C&L Inventory of ECHA the following H-statements have been notified for maltol: H302 (1608 of 1938 notifiers, corresponding to 82.97%), H319 (105 of 1938 notifiers, corresponding to 5.42%), H315 (116 of 1938 notifiers, corresponding to 5.99%), H335 (101 of 1938 notifiers, corresponding to 5.21%). The C&L Inventory contains three more hazard statements for maltol with notification percentages of < 0.1% each. They were omitted in this comment. In table 2 two hazard statements have been mentioned with notification percentages of 5.42% to 82.97%. Is there a reason for the omission of H315 with a notification percentage of 5.99%? Is there a reason for the omission of H335 with a notification percentage of 5.21%?

Ethyl vanillin: Table 2 states H302, H315 and H319. According to the C&L Inventory of ECHA, the following H-statements have been notified for ethyl vanillin: H302 (66 of 1938 notifiers, corresponding to 3.41%), H315 (55 of 1938 notifiers, corresponding to 2.84%), H319 (315 of 1938 notifiers, corresponding to 16.25%), H335 (55 of 1938 notifiers, corresponding to 2.84%). In table 2 three hazard statements have been mentioned with notification percentages of 2.84% to 16.25%. Is there a reason for the omission of H335 with a notification percentage of 2.84%?

Furaneol: Table 2 states H302, H314, H317 and H319. According to the C&L Inventory of ECHA the following H-statements have been notified for furaneol: H302 (508 of 1817 notifiers, corresponding to 27.96%), H314 (59 of 1817 notifiers, corresponding to 3.25%), H317 (1397 of 1817 notifiers, corresponding to 76.88%), H319 (1338 of 1817 notifiers, corresponding to 73.64%) and H318 (58 of 1817 notifiers, corresponding to 3.19%). In table 2 four hazard statements have been mentioned with notification percentages of 3.25% to 76.88%. Is there a reason for the omission of H318 with a notification

percentage of 3.19%?

Methyl cyclopentenolone: Table 2 states H302. According to the C&L Inventory of ECHA the following H-statements have been notified for methyl cyclopentenolone: H302 (49 of 1731 notifiers, corresponding to 2.83%), H317 (35 of 1731 notifiers, corresponding to 2.02%), H318 (35 of 1731 notifiers, corresponding to 2.02%), H315 (38 of 1731 notifiers, corresponding to 2.20%), H319 (38 of 1731 notifiers, corresponding to 2.20%), H334 (38 of 1731 notifiers, corresponding to 2.20%), and H335 (38 of 1731 notifiers, corresponding to 2.20%),. In table 2, one hazard statement has been mentioned with notification percentages of 2.83%. Is there a reason for the omission of H317 and H318 with notification percentages of 2.02%, each? Is there a reason for the omission of H315, H319, H334 and H335 with notification percentages of 2.20%, each?

42 Schulz
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Federal
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for Risk
Assessmen
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6.4 Chemical
ingredients in e-
liquids

p. 24, table 2
Specific comments on table 2, if the column on CLP will be retained
Isoamyl acetate: Table 2 states H226. According to the C&L Inventory of ECHA the follow-ing H-statements have been notified for isoamyl acetate: H226 (2807 of 2810 notifiers, corresponding to 99.89%) and H335 (38 of 2810 notifiers, corresponding to 1.35%). The C&L Inventory contains three more hazard statements for isoamyl acetate with notification percentages of < 0.1% each. They were omitted in this comment. In table 2 one hazard statements has been mentioned with a notification percentage of 99.89%. Is there a reason for the omission of H335 with a notification percentage of 1.35%?

Acetic acid: Table 2 states H226 and H314. According to the C&L Inventory of ECHA the following H-statements have been notified for acetic acid: H226 (4871 of 4887 notifiers, corresponding to 99.67%), H314 (4874 of 4887 notifiers, corresponding to 99.73%), H318 (699 of 4887 notifiers, corresponding to 14.30%), H332 (74 of 4887 notifiers, corresponding to 1.51%), H312 (67 of 4887 notifiers, corresponding to 1.37%) and H335 (20 of 4887 notifiers, corresponding to 0.41%). The C&L Inventory contains four more hazard statements for acetic acid with notification percentages of

Please see reply to comment 34. The Opinion has been revised.

< 0.11% each. They were omitted in this comment. In table 2 two hazard statements have been mentioned with notification percentages of 99.67% to 99.73%. Is there a reason for the omission of H318 with a notification percentage of 14.30%? Is there a reason for the omission of H332 with a notification percentage of 1.51%? Is there a reason for the omission of H312 with a notification percentage of 1.37%? Is there a reason for the omission of H335 with a notification percentage of 0.41%?

The mistake in the labelling of harmonised classification has already been explained above.

Benzyl alcohol: Table 2 states H302 and H319. According to the C&L Inventory of ECHA the following H-statements have been notified for benzyl alcohol: H302 (5125 of 5127 notifiers, corresponding to 99.96%), H319 (1244 of 5127 notifiers, corresponding to 24.26%), H332 (5025 of 5127 notifiers, corresponding to 98.01%), H312 (687 of 5127 notifiers, corresponding to 13.40%) and H315 (40 of 5127 notifiers, corresponding to 0.78%). The C&L In-ventory contains one more hazard statement for benzyl alcohol with a notification percentage of < 0.1%. It was omitted in this comment. In table 2 two hazard statements have been mentioned with notification percentages of 24.26% to 99.96%. Is there a reason for the omission of H332 with a notification percentage of 98.01%? Is there a reason for the omission of H312 with a notification percentage of 13.40%? Is there a reason for the omission of H315 with a notification percentage of 0.78%?

The mistake in the labelling of harmonised classification has already been explained above.

Menthol: Table 2 states H315 and H319. According to the C&L Inventory of ECHA, the following H-statements have been notified for menthol: H315 (2054 of 2108 notifiers, corresponding to 97.44%), H319 (1770 of 2108 notifiers, corresponding to 83.97%), H318 (48 of 2108 notifiers, corresponding to 2.28%) and H335 (48 of 2108 notifiers, corresponding to 2.28%). The C&L Inventory contains one more hazard statement for menthol with a notifica-tion

			percentage of < 0.15%. It was omitted in this comment. In table 2 two hazard statements have been mentioned with notification percentages of 83.97% to 97.44%. Is there a reason for the omission of H318 and H335 with notification percentages of 2.02%, each?	
43	Schulz Thomas, German Federal Institute for Risk Assessment, Germany	6.4 Chemical ingredients in e-liquids	<p>p 24, table 2</p> <p>Specific comments on table 2, if the column on CLP will be retained</p> <p>Hexyl acetate: Table 2 states H226. According to the C&L Inventory of ECHA, the following H-statements have been notified for hexyl acetate: H226 (1806 of 1900 notifiers, corresponding to 95.05%), H315 (9 of 1900 notifiers, corresponding to 0.47%) and H319 (9 of 1900 notifiers, corresponding to 0.47%). The C&L Inventory contains three more hazard statements for hexyl acetate with notification percentages of < 0.12% each. They were omitted in this comment. In table 2 one hazard statement has been mentioned with a notification percentage of 95.05%. Is there a reason for the omission of H315 and H319 with notification percentages of 0.47%, each?</p>	Please see reply to comment 34. The Opinion has been revised.
44	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.4 Chemical ingredients in e-liquids	<p>Page 23 / Lines 33-35</p> <p>We question why SCHEER relies on partial data and not on the EU-CEG data and how SCHEER determined that this partial data was in fact representative of the EU market in general.</p>	SCHEER used relevant data available for its assessment. These data show that the ingredients used in the Netherlands and in Greece are probably representative for the EU market in general.
45	No agreement to disclose personal data	6.4 Chemical ingredients in e-liquids	P.23, 133: The studies carried out in the Netherlands and Greece are neither updated, nor representative of the chemical ingredients that are actually present in products sold in other Member States. This is mainly due to the fact that specific regulations derived from TPD transposition may be in force in such Countries.	SCHEER used relevant data available for its assessment. These data show that the ingredients used in the Netherlands and in Greece are probably representative for the EU market in general.
46	Folmann Hempler Nana, Danish Society of Public	6.5 Assessment of Health Risks	<p>We would like to comment on the SHEER on health effects of electronic cigarettes (e-cigarettes): Regarding the conclusions in section 5. We agree with the conclusion on CNS. We also agree that there, in general, is lack of long-term data. However, we think that the</p>	Please see Table 1, answer 10.

Health,Den
mark

conclusion on pulmonary disease is confusing/weak.

To our best knowledge, there exist as much long-term data on pulmonary disease as on cardiovascular disease, and in both cases the evidence shows that there probably is an increased risk of disease by long-term exposure.

In vivo experiments as well as animal studies have demonstrated airway inflammation and remodeling/scarring 1 2 3 4 5 and impairments in lung function 6 7. Exposure to e-cigarette fluid promoted respiratory viral infection 8 and bacteria became more virulent when exposed to e-cigarette vapour 4. Human experiments have shown airway obstruction⁹, induced transient lung inflammation and gas exchange disturbances 10 and dysregulation in normal human lung homeostasis after short-term inhalation 11. A study studying sputum of e-cigarette users found altered profile of innate defense proteins in airway secretions, inducing similar and unique changes relative to cigarette smoking 12. Another human study found that chronic vaping disrupts the protease-antiprotease balance by increasing proteolysis in lung, which may place vapers at risk of developing chronic lung disease 13. Animals exposed to e-cigarette vapor showed a disorganization of alveolar and bronchial epithelium 14 and higher mortality when exposed to virus infection and neonatal exposure showed impairment in postnatal lung growth. Animals exposed to chronic vaping developed asthma, COPD⁷ and lung cancer 15. In addition, there is moderate evidence from population based studies for increased lung symptoms in adolescents and adults and an increase in asthma exacerbations 16 17 18 19 20 21 . Even in adolescent never-cigarette users, risk of bronchitic symptoms has been found to be significantly elevated, after adjustment for relevant potential confounders 22. Longitudinal studies have shown increased risk of COPD exacerbations 23 and incident respiratory disease 18.

Already in 2017 a review concluded 24: “There is a rapidly growing body of evidence derived from in vitro, animal, and human studies that e-cigarette use may have significant pulmonary toxicity”.

A recent review concluded 25: “Inhalation of e-cigarette aerosols

impacts pulmonary physiology, with short-term exposure leading to increased airway reactivity, while long-term exposure leads to increased airway resistance, airway obstruction and inflammation. Both short-term (weeks to months) and long-term (years to decades) inhalation of e-cigarette aerosols increase lung inflammation and airway reactivity, raising the concern that vapers will develop asthma, chronic obstructive lung disease (COPD) and chronic bronchitis”.

Another recent review (on pulmonary health) concluded 26: “Studies show measurable adverse biologic effects on organ and cellular health in humans, in animals, and in vitro”. “We conclude that current knowledge of these effects is insufficient to determine whether the respiratory health effects of e-cigarette are less than those of combustible tobacco products”.

A newly published study found that among never tobacco users, the adjusted odds of reporting lung disease (diagnosed with COPD, emphysema, or chronic bronchitis) were more than 4 times higher among everyday e-cigarette users than among never e-cigarette users 27. The study had adjusted for 15 sociodemographic and health behavior factors.

SHEER recognizes that e-cigarettes are toxic to the pulmonary system. However, it is difficult for those who are not health professionals to understand the meaning.

47	Monti Denis,DE MOVAP,F rance	6.5 Assessment of Health Risks	<p>You said lines 13 et 14 : (Translate in French as answer is my comments are in French "Les risques de problèmes cardio-vasculaires dus au vapotage sont forts."</p> <p>My comments : Une étude menée en 2014 , ayant pour but de comparer les « risques potentiels liés à l'utilisation des cigarettes électroniques, par rapport aux effets dévastateurs bien établis du tabagisme » explique dans ses conclusions que les preuves actuellement disponibles indiquent que « les cigarettes électroniques sont de loin une alternative moins nocive au tabagisme » et que « des avantages importants pour la santé sont attendus chez les fumeurs qui passent du tabac aux cigarettes</p>	Please see Table 1, answer no 2.
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			électroniques ref:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/	».	
48	No agreement to disclose personal data	6.5 Assessment of Health Risks	Il est aberrant de soutenir que le vapotage est dangereux pour le système cardio vasculaire, si le vapotage est dangereux, le tabagisme lui en est mortel. Cessez de servir la soupe aux entreprises du tabac, faites preuve d'honnêteté et de courage, la cigarette électronique est le moyen du 21 siècle, de mettre un terme au génocide planétaire qu'est le tabac, vous serez jugés coupable, d'avoir fait en sorte de ne pas faciliter l'accès à la cigarette électronique, au plus grand nombre, surtout aux plus démunis. Vous n'avez donc pas de conscience ?! il vous faudra répondre de vos actes et de vos décisions qui vont à l'encontre de la plus basique des politiques de santé.		Please see Table 1, answer no 1.
49	cassalia andreina,just gold di romeo antonio raffaele,Italy	6.5 Assessment of Health Risks	bassissimo rischio		Thank you for your comment.
50	Ollila Eeva,Cancer Society of Finland,Finland	6.5 Assessment of Health Risks	The preliminary SHCEER opinion deserves to be commended on its thorough review of the existing scientific and other literature on e-cigarettes and their safety, it remains somewhat unclear, how well the SCHEER opinion captures all major risks involved, as not all the ingredients are known, flavours, metals and ultrasmall particles are not part of the risk assessment. Flavours are known to significantly affect the toxicity of e-cigarettes (see for example Leigh et al 2016). It is alarming is that the safety of flavours has in most cases been tested only for per oral use, not when heated and inhaled (see also Stratton et al 2018), although it is clear that heating results in new chemical compounds. It has been earlier postulated that especially sweet flavours would cause irritation in mouth and respiratory track (for example Lerner et al 2015). While it is understandable that it is not possible to give a scientific opinion on the health effects of the ultrasmall particles, as there was no available data, this is also concerning, as it has been postulated that the ultrasmall particles can be especially harmful as they can enter		Please see the reply to comment 38. The Opinion has been amended accordingly.

especially deep in the lung tissue and further from there to the rest of the body.

While the device type and power level remain largely unregulated in EU, the opinion notes that later generation models can be used at much higher power and newest pod-mods contains nicotine salts enabling users to consume increased levels of nicotine.

Ref: Leigh NJ, Lawton RI, Hershberger PA, et al. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ends). *Tobacco Control* 2016;25:ii81–7. <http://dx.doi.org/10.1136/tobaccocontrol-2016-053205>
 Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. *PLoS One* 2015;10:e0166732.
 Stratton K, Kwan LY, Eaton DL. Public health consequences of e-cigarettes. A consensus study report of the National academies of sciences, engineering and medicine. USA: The National Academic Press, 2018

51	CHampagnac Maxime,Phode,France	6.5 Assessment of Health Risks	<p>p31 lines 23-25</p> <p>"The levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavours, and tobacco alkaloids in electronic cigarette aerosols vary greatly (Cheng, 2014)," https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p> <p>The sources used in this report shouldn't be partially used as it is in contradiction with (Cheng, 2014) as Yobacco alkaloids are not always present "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids. "</p>	Please see Table 1, answer 4.
52	Poirson Philippe,Sovape,France	6.5 Assessment of Health Risks	<p>[p. 26 l. 28-47] American datas are not relevant for EU situation. Chapter 5 specifies that this SCHEER report concerns only nicotine vaping, but the American data presented here do not distinguish between the different types of vaping used, with only flavours, with nicotine or with cannabinoids. Nearly half of the US data on “young current vaping users” could be about THC use (Farsalinos 2020), which is prohibited in most European countries and is in any case not covered by the TPD. These data are not relevant to the subject of the report. Moreover, US measurements of frequency of use make these data very low reliable.</p>	Please see Table 1, answer 8. The review papers used in the Opinion does not only cover US data, but data from European studies as well as other studies around the world. What matters is the scientific reliability of the research sources; the information included in the review papers disucssed in the Opinion reflects up-to-date data on the effects of electronic cigarettes on human health.

53	CHATZIA POSTOLOU PANAGIOTIS,PRIVATE OFFICE PRIVATE HOSPITAL,Greece	6.5 Assessment of Health Risks	<p>Use European robust data as Chyderiotis 2020 would be more relevant to the purpose of this report on vaping in the TPD context. age 49 , lines 1-20</p> <p>The impact of E-Cigarettes vs the traditional smoking use, should be also included at the SCHEER Preliminary Opinion. Evidences indicating a significant reduction in respiratory symptoms and COPD exacerbations are very promising and should be included in the analysis. For example the study of Polosa 2018 (Health effects in COPD smokers who switch to electronic cigarettes a retrospective prospective 3years follow up), shows significant improvements in COPD exacerbation rates, CAT scores, and 6MWD in the E-Cigarettes user group over the 3-year period (p<0.01).</p> <p>Page 49 , lines 4-6</p> <p>Several experimental studies evaluating the exposure of human bronchial epithelial cells either to E-Cigarette or to Cigarette Smoke have shown positive results for E-cigarettes. An example of these studies is uploaded (Scheffler 2015 Evaluation of E-Cigarette Liquid Vapor and Mainstream Cigarette Smoke after Direct Exposure of Primary Human Bronchial Epithelial Cells) Based on the results of this study, the viability of mainstream smoke cigarette exposed cells was 4.5–8 times lower and the oxidative stress levels 4.5–5 times higher than those of e-cigarette vapor exposed cells, depending on the donor.</p> <p>Ref: Scheffler (2015) Evaluation of E-Cigarette Liquid Vapor and Mainstream Cigarette Smoke after Direct Exposure of Primary Human Bronchial Epithelial Cells</p>	Please see Table 1, answer 1.
54	No agreement to disclose personal data	6.5 Assessment of Health Risks	<p>STRINGENT PRODUCT TESTING AND SAFETY STANDARDS SHOULD BE A REQUIREMENT PRIOR TO MARKET ENTRY</p> <p>SCHEER has missed an opportunity to highlight that not all e-cigarette products and e-liquids are manufactured to the same high quality and safety standards, and there is great disparity in the quality of products on the market, particularly in the US, which is the source of the majority of the cited data. Responsible manufacturers undertake comprehensive scientific work to understand the potential impact of product use on adult smokers' health. Formal assessment of product safety should be carried out as a requirement, and would ensure that products reaching the</p>	Please see the Table 1, answer 8. Formal assessment of product safety is not within the remit of the SCHEER.

market for sale are legally compliant with technical product regulation and assured from a safety perspective.

SCHEER’S STATEMENT IS NOT UNEXPECTED AND IS THE BASIS OF TOXICOLOGY

This paragraph is short and lacks clear purpose, it merely states that “mainly chemicals present in the aerosol are responsible for possible health effects for users of electronic cigarettes”. As noted elsewhere, the Opinion fails to consider how the presence and levels of chemicals in e-cigarette aerosols compare to combustible tobacco smoke. A recent systematic review has shown that e-cigarettes (including the ingredients used in e-liquids) are substantially less toxic than comparable use of cigarettes or solutions, which is the most relevant comparison for adult smokers[1].

“The EU Injury Database (IDB) does not know (yet) the relatively new product “electronic cigarette”” and it would be beneficial to collect this information. Yet later in the Opinion the Rapid Alert System for Non-Food Consumer Products (RAPEX) is discussed (Ref pg 53 line 45): 54 cases over 14 member states, and it appears as though earlier version content is also in this report. It should be noted, that there were 54 cases reported over 10 years across the EU which represents a very low incidence of reports to RAPEX. Furthermore, the IDB is not the only source of information on e-cigarette injuries, as case studies on injury and poisoning through device malfunction, unintended, improper or irresponsible use are published in the scientific literature – which should also be reviewed.



6.5.5_Risk_assessment.pdf

Please see the Table 1, answer 1.

Over the past few years a series of projects have been initiated by EuroSafe with the support of the European Commission to improve national infrastructures and enhance injury data collection at accident and emergency departments at hospitals. This led to the creation of the European Injury Data Base by the network of IDB-data collecting countries.

In contrast, the (RAPEX) Safety Gate rapid alert system enables quick exchange of information between EU/EEA member states, the UK and the European Commission about dangerous non-food products posing a risk to health and safety of consumers e.g. for non-compliance with legal requirements.

55	Serafimov Lubomir, Bulgarian Vape Association	6.5 Assessment of Health Risks	The assessment gives a view on the strength of evidence about various risks. But the strength of evidence differs from the likelihood a user will experience something or how much harm it does. There could be for example strong evidence of a rare occurrence of a minor irritation to the respiratory system, so the
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Please see Table 1, answer 3.

	<p>n of Manufacturers, Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E- liquid,Bulgaria</p>		<p>SCHEER Opinion provides no real quantification of risk and thus it is of little value to policymakers. When presented with different assertions about risk, policymakers should be able to understand whether it is a big or a small risk. While statements in the Opinion like “may cause cancer” provide practically no policy-relevant information. The opinion gives no idea about the seriousness of the risks it discusses.</p> <p>There is a study (Mortality in relation to smoking) that shows even in the case of smoking, with extremely high toxic exposures, users avoid nearly all the lifetime mortality risk of smoking if they quit by age 40, perhaps after 20 years smoking. The question is what would these mortality rates look like for the vastly lower exposures arising from years of vaping (using electronic cigarettes)? The Opinion typically looks at markers of exposure or risk and leaps to a conclusion about potential harm.</p> <p>The use of nicotine, a mild recreational drug, intentionally creates a variety of effects on the body, including on the cardiovascular system. However, long term epidemiological studies of nicotine use without smoke inhalation, for example through the use of nicotine gum or snus, do not show serious health effects.</p> <p>Ref. uploaded: Doll (2004). Mortality in relation to smoking: 50 years’ observations on male British doctors.</p>	<p>Please see Table 1, answer 1.</p>
<p>56</p>	<p>Loddenkemper Robert, German Respiratory Society (DGP), Germany</p>	<p>6.5 Assessment of Health Risks</p>	<p>The overall weight of evidence for health risk of e-cigarettes use to the respiratory tract and the lung is in my opinion meanwhile more than moderate.</p> <p>Please, find attached an overview of older and recent references including short comments on the results of the studies. and in order of different topics (short term effects, long term effects (human, animal and cell studies): respiratory symptoms, asthma, bronchitis, COPD, proinflammatory response, response of the immune system including viral/bacterial infections, COVID-19, EVALI, cancer.</p> <p>Futhermore I include few studies on second-hand exposure.</p>	<p>Please see Table 1, answer 10.</p>



To_SCHEER-Health_risks_of_e-cigarette_to_

57	Compernelle Thomas, British American Tobacco, Belgium	6.5 Assessment of Health Risks	<p>In SCHEER’s Preliminary Opinion, the approach to risk assessment does not take into account the public health principle of tobacco harm reduction and therefore results in an outcome that is inconsistent with the available evidence. (LN37-38) states that “chemicals present in the aerosols are responsible for the health effects”; however, SCHEER fail to acknowledge the overall reductions in chemicals present (toxicants and carcinogens) in e-cigarette aerosols compared to cigarettes that has led to widespread agreement amongst experts and public health authorities that vaping is less risky than smoking (1-4). The Opinion looks to identify whether there is any residual risk with e-cigarettes and does not look at a balance of risks. It is already widely accepted that vaping is not risk-free (1-3), so a SCHEER report concluding only that will not be helpful. Data in the EU show regular e-cigarette use by never smokers remains very rare (3,5-11) and similar to that of licensed nicotine products (12). Using e-cigarettes as a way of quitting smoking is actively encouraged in several EU Member States (3,13-15). This section should therefore, in addition to characterising the residual risk from vaping, investigate the risk reduction to the user when switching from smoking to vaping. The relevance of this to public health in the EU should then be put into context by considering transitions between smokers, vapers and non-users.</p> <p>(LN 44-45): SCHEER suggest they consider epidemiological or clinical trials on e-cigarettes to inform their assessment of health risk, yet their conclusion is at odds with the current evidence. A number of studies have shown the reduction in exposure biomarkers in smokers when switching to e-cigarettes (16-17).</p> <p>(LN47-48): with regards to youth vaping, sales to minors are already prohibited and a review of the science assessing enforcement efficacy and various potential new measures to reduce youth access and use would be relevant to inform the Commission’s policy development thinking.</p>
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Please see Table 1, answer 1.

(LN49): the risks of injuries and burns from e-cigarettes when contextualized with injuries and burns from other products, are far lower. Regulated e-cigarette products are covered directly by the CE marking directives of EMC (2014/30/EU) and RoHS (2011/65/EU) and then by aspects of the General Product Safety Directive (2001/95/EC) (18-20).

We respectfully request SCHEER to review their risk assessment approach, considering the available evidence and risk of e-cigarettes relative to cigarettes including taking into account the attached literature.



ref-57.docx

58 Posch Waltraud, Austrian Association of Addiction Prevention, Austria 6.5 Assessment of Health Risks We'd like to emphasize the potential for harm which is associated with electronic cigarettes. They have to be seen at their own or in comparison with non-consumption. Tobacco industry always compares them with combustible tobacco. That's a misleading comparison. Seen as their own, electronic cigarettes seem to be risky for health. This is even more true when you compare them to non-consumption.

Please see Table 1, answer 1.

As the Austrian Association for Addiction Prevention we also focus on the potential for an addiction to develop or be sustained. Electronic cigarettes are made to contain nicotine. Nicotine is highly addictive.

Seen from Addiction Prevention it's neither possible to call electronic cigarettes harmless nor to call them safe. Their hazard profile includes the potential of addiction as well as the potential to harm human health.



6.5_Assessment_of_health_risks_Electronic-

59	Dahlmann Dustin,Independent European Vape Alliance,Germany	6.5 Assessment of Health Risks	<p>P47 L13-26 The Committee reports that some users experience irritation and cough, citing Polosa (2011). In fact, this study is careful to point out that these minor AEs "decreased substantially" by week 24. From week 4 to 24 the occurrence of minor AEs decreased in every reported measure: throat irritation (23.4 to 14.8%); mouth irritation (20.6 to 7.4%); dry cough (32.4 to 11.1%). Most importantly, there were zero serious Adverse Events reported in Polosa et al. Polosa and colleagues also draw attention to the fact that side effects most commonly reported in trials for drugs for nicotine dependence are totally absent.</p> <p>P49 L2-20 All of the citations are in vitro studies in which there was no combustible cigarette control and which used EC aerosol exposure that wasn't relevant to human use. This led Li Volti et al (2018) to say of such studies: "The present study does not replicate normal conditions of use and lacks standardized protocols for E-cigarette aerosol exposure and dosimetry. To this regard, animal studies and in vitro systems often include chronic, high-dose exposures and do not approximate the type of exposure from human vaping, thus leading to extreme overestimation of toxicological effects" xx</p> <p>The review here fails to consider the health impact on smokers with chronic lung conditions. As Polosa (2016), in a study of COPD patients who smoke, found:</p> <p>"A marked reduction in cigarette consumption was observed in ECs users. A significant reduction in COPD exacerbations was reported in the COPD EC user group, their mean (\pmSD) decreasing from 2.3 (\pm1) at baseline to 1.8 (\pm1; $p = 0.002$) and 1.4 (\pm0.9; $p < 0.001$) at F/up1 and F/up2 respectively. A significant reduction in COPD exacerbations was also observed in ECs users who also smoked conventional cigarettes (i.e. 'dual users'). COPD symptoms and ability to perform physical activities improved statistically in the EC group at both visits, with no change in the control group."</p> <p>P51 L27-57</p>	Results of the study by Polosa et al (2011) have been rephrased in the final Opinion.
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Current evidence unequivocally demonstrates that the air concentrations of potential toxicants are far below various internationally accepted thresholds after unrestricted vaping in closed rooms; and, of course, significantly lower than that emitted from cigarettes.

Ref:

McAuley, T. R et al (2012)

O'Connell, G. et al (2015)

Logue, J. M. et al (2017)

Liu, J. et al (2017)

van Drooge, B. L. et al (2019)

Schober, W. et al (2019)

Shearston et al (2019) is not evidence that ECs cause secondhand exposure; it is a protocol for a study which has not yet reported any findings.

P52

L5-10

Diez-Izquierdo (2018) is a review in which the only in-home (natural setting) test showed no significant differences in nicotine levels on surfaces in the homes of ENDS users compared to non-smokers/non-ENDS users.

P55

L7-13

SCHEER states that the "weight of evidence concerning effects of second-hand exposure of children and adolescents cannot be established as there exists a complete paucity of evidence regarding the acute and long term effects on cardiovascular and other health outcomes in this group."

While true, the same statement would apply to the vapor of heated cooking pots or the odor of perfume. This is because there is no rationale for investigating the effects of emissions lacking significant amounts of potentially harmful substances on health outcomes. This context and perspective is important when framing the lack of evidence.



Assessment_of_Health_Risks.pdf

60	Juchtmans Michael, VapeBel (Independent Belgian Vape Federation, Belgium)	6.5 Assessment of Health Risks	<p>More and more leading health experts and governments recognize the important role that significantly less harmful alternatives such as the electronic cigarette can play in reducing smoking, also in Belgium. For example, the Anti-Cancer Foundation, the VIGEZ or the Superior Health Council recently endorsed the usefulness of the electronic cigarette as a smoking cessation agent. Also, governments, seen as leading the way in tobacco control policies, are increasingly adopting regulations in favor of less harmful alternatives based on a “Harm Reduction” philosophy. This is the case in the United Kingdom, New Zealand and Norway, among others.</p> <p>It is often alluded that electronic cigarettes are a stepping stone to smoking or attractive to young people. The latest figures from, for example, Sciensano's 2018 Health Interview Survey completely invalidate these claims. These figures show that only 0.5% of young people between 15 and 24 years old use the electronic cigarette on a daily basis and that only five in a thousand people in the population use the e-cigarette, although they had never smoked tobacco before.</p> <p>The diversity of flavors is also cited as a potential problem. There is no scientific basis for this. On the contrary, the diversity of available flavors is an asset to permanently deter smokers from smoking and to avoid relapse. Although a large number of smokers initially switch to the electronic cigarette via a tobacco aroma, they often opt for other flavors afterwards. This helps them differentiate the use of an electronic cigarette from traditional smoking and reduce the risk of them reverting to smoking.</p> <p>We therefore argue for a regulation that on the one hand stimulates smokers who cannot be put off the cigarette to switch to less harmful alternatives and, on the other hand, limits the risk of young people and non-smokers starting as much as possible. Such legislation should make an “evidence-based” clear differentiation based on the risk profile of the products and not on unfounded arguments and disinformation.</p> <p>There should be a framework that allows market actors to bring</p>	<p>Please see Table 1, answer 1.</p> <p>Please see Table 1, answer 5.</p> <p>Please see Table 1, answers 1 and 7.</p> <p>This is outside of the remit of the SCHEER (risk management).</p> <p>This out of the scope of the Opinion.</p>
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significantly less harmful alternatives, such as the electronic cigarette, to the attention of smokers and that allows correct and scientifically based information on less harmful alternatives. Not a further curtailment of it. Simply harmonizing all products only strengthens the position of the most widespread and harmful among them, namely the cigarette smoked during combustion.

As active players in the industry, we are extremely disappointed that neither of us was asked to take a position. Neither for the scheduled hearings, nor by written means. Of course we remain available at all times if this is still possible.

The public consultation was indeed the opportunity for any stakeholders (including industry) to comment on the SCHEER preliminary Opinion.

61	Miotla Pawel, 2nd Department of Gynecology, Medical University of Lublin, Lublin, Poland, Poland and	6.5 Assessment of Health Risks	<p>Page 50, line 4</p> <p>I would like to add this writing by me few sentences considering smoking during lactation: "Nicotine delivered to the mother's organism with traditional cigarettes can be rapidly absorbed during breastfeeding by the intestine of the infant and may lead to numerous, dangerous conditions, including apnea, hypoxia or restlessness. [Primo CC, Ruela PB, Brotto LD, Garcia TR, Lima Ede F. Effects of maternal nicotine on breastfeeding infants. Rev Paul Pediatr. 2013; 31: 392–397.]</p> <p>Study conducted on animal model showed that waterpipe tobacco smoke exposure during lactation altered the milk composition and lipid profile as well. WTP was also associated with disturbances of glucose homeostasis and hormonal levels in dams and pups. [Maternal waterpipe tobacco smoke exposure during lactation induces hormonal and biochemical changes in rat dams and offspring. Al-Sawalha NA, Gaugazeh HT, Alzoubi KH, Khabour OF. Basic Clin Pharmacol Toxicol. 2020 Sep 18. doi: 10.1111/bcpt.13493.]</p> <p>On the current stage there is no evidence that electronic cigarettes can be consider as safer for breastfeeding mother and newborn. It has been already published that breastfeeding is positively associated with smoking abstinence in puerperium and continuing this abstinence should be recommended to all lactating women. [Einarson A, Riordan S. Smoking in pregnancy and lactation: a</p>	<p>Although these are all valid papers, traditional smoking is out of the scope of this Opinion. Please see table 1, answer 1.</p>
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			review of risks and cessation strategies. Eur J Clin Pharmacol 2009;65:325-30.]"		
62	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.5 Assessment of Health Risks	<p>Page 25 / Lines 47-48</p> <p>SCHEER notes poisoning from ingestion of nicotine, particular for young children, as a potential health effect. SCHEER should also take note of the fact that the TPD recognizes this risk and has enacted several provisions that reduce the risk of accidental poisoning.</p> <p>Specifically, Art. 20.3(a) and (b) mandates that Member States limit the size of refill containers (maximum 10 ml in volume) as well as the nicotine strength (20 mg/ml limit). These mandates both serve to reduce the risk of accidental poisoning. In addition, Art. 20.3(g) requires that "electronic cigarettes and refill containers are child- and tamper-proof, are protected against breakage and leakage and have a mechanism that ensures refilling without leakage."</p> <p>Page 25, lines 44-45</p> <p>Whenever SCHEER refers to data (here, data on health impacts), it should make clear the origin of the data so that a determination can be made of the impact on the EU, especially given that the markets and products in the EU are very different from markets and products in non-EU countries, such as the US. This will also allow for an appropriate weighting of risk assessment data in connection with data from the EU versus data from non-EU countries.</p>	<p>The SCHEER agrees that the directive and especially art 20(3) (a, b, g) are meant to limit the risk of accidental poisoning. The lines referred to are in the introduction of the assessment of the health risks (6.5), two paragraphs aiming to explain the SCHEER strategy / different lines followed.</p> <p>In section 6.5.4 evidence of human health impact is given, based on published studies. In section 'Electronic cigarette nicotine poisonings' P50 lines 26-40 focus is on poisoning of children due to ingestion of e-liquid. Here sufficient detail can be found in this issue.</p>	Please see Table 1, answer 8.
63	No agreement to disclose personal data	6.5 Assessment of Health Risks	P.25, 147: ANAFE believes that the directive is absolutely fit to protect children from the ingestion of products containing nicotine; as a matter of fact, there is an obligation to equip bottles with childproof systems (the same systems used for much more dangerous products) and this rule, as recognised in other passages of the Opinion, is effective.	<p>The SCHEER agrees that the directive and especially art 20(3) (a, b, g) are meant to limit the risk of accidental poisoning. The lines referred to are in the introduction of the assessment of the health risks (6.5), two paragraphs aiming to explain the SCHEER strategy / different lines followed.</p> <p>In section 6.5.4 evidence of human health impact is given, based on published studies. In section 'Electronic cigarette nicotine poisonings' P50 lines 26-40 focus is on poisoning of children due to ingestion of e-liquid. Here sufficient detail can be found in this issue.</p> <p>No change in the Opinion needed.</p>	
64	Froguel Alizee, Cancer Research UK, United Kingdom	6.5 Assessment of Health Risks	Further research is needed to determine the long-term health effects of e-cigarette use. E-cigarettes are a relatively new product – they are not risk free and shouldn't be used by people who have never smoked. However, research to date has found that they are much less harmful than smoking. (1-7) When monitoring evidence e-cigarettes harms, Cancer Research UK only considers systematic reviews, randomised control trials, cohort and case control studies	<p>This comment states that "Cancer Research UK believe that evidence on the long-term cardiovascular effects of nicotine in e-cigarettes is limited.", which is in fact what we have also stated in the Opinion.</p>	

and do not consider research with tobacco industry links. Some studies cited in this section don't meet this criteria.

The report cites a European Heart Network document, which finds mixed evidence for the short-term cardiovascular effects of e-cigarettes but that e-cigarettes are likely less harmful to the cardiovascular system than cigarettes. The report also states that e-cigarettes' long-term cardiovascular effects are still unknown due to lack of relevant data. They conclude that there is an urgent need for more long-term evidence.

Please see Table 1, answer 1.

Based on the lack of long-term data, Cancer Research UK conclude that the overall weight of the risk of long-term systemic effects on the cardiovascular system is limited. Long-term cardiovascular effects should not be determined by studies looking at acute changes, but need to include studies examining long-term impacts. Other substances (i.e. caffeine) have an acute effect on heart rate but are deemed safe for human consumption. We agree that the cardiovascular effects of e-cigarettes is an outstanding question and longer-term studies are needed to determine the full effect on the cardiovascular system.

Evidence so far suggests that switching from smoking to vaping can benefit cardiovascular function. A systematic review found no long-term effects of switching from smoking to vaping on heart rate but found a significant reduction in systolic and diastolic blood pressure.⁽⁸⁾ A recent trial also compared cardiac outcomes in adult smokers who either switched to nicotine e-cigarettes, non-nicotine e-cigarettes or continued to smoke. It found significant improvements in arterial function between the tobacco control and both e-cigarette groups but found no difference between the two e-cigarette groups.⁽⁷⁾

Cancer Research UK believe that evidence on the long-term cardiovascular effects of nicotine in e-cigarettes is limited. Evidence from people who have used nicotine replacement therapy products for years shows no increase in their risk of cardiovascular disease.⁽⁸⁾ Given the current absence of long-term data, Cancer Research UK conclude that there is limited evidence of long-term

systemic effects of e-cigarettes on the cardiovascular system and more robust long-term research is essential.

References:

1. Gualano, et al.(2014) Electronic cigarettes: assessing the efficacy and the adverse effects through a systematic review of published studies.
2. Caponnetto, et al.(2013) Efficiency and Safety of an eElectronic cigarette (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study.
3. Burstyn(2014) Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks.
4. Goniewicz, et al(2013) Levels of selected carcinogens and toxicants in vapour from electronic cigarettes.
5. McNeill, et al.(2018) Evidence review of e-cigarettes and heated tobacco products. Commissioned by Public Health England
6. Skotsimara, et al.(2019) Cardiovascular effects of electronic cigarettes: A systematic review and meta-analysis.
7. George, et al.(2019) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes.
8. Murray, et al.(1996) Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study.

65	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	6.5 Assessment of Health Risks	<p>Page 26, lines: 27-47</p> <p>The SCHEER opinion cites studies mainly from the US and draws unrepresentative conclusions for the EU, ignoring available, more recent data from the EU.</p> <p>In fact, a number of studies in the EU have shown relatively low use of e-cigarettes by adolescents. It is also important to distinguish between regular use and ever use (ever use does not mean the regular use, it rather means the experimental trials). Therefore, ever use should not be the basis for the exposure assessment.</p> <p>Ref: Brožek, G., et al. (2018). The prevalence of e-cigarette and cigarette smoking among students in Central and Eastern Europe - preliminary results of YUPESS study. 52(suppl 62): PA4543.</p> <p>https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6651674/</p>	Please see Table 1, answer 8.																																				
66	Cipri Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.5 Assessment of Health Risks	<table border="1"> <tr> <td>P</td> <td>47/</td> <td>L</td> <td>13</td> <td>-</td> <td>16</td> </tr> <tr> <td>P</td> <td>49/</td> <td>L</td> <td>2</td> <td>-</td> <td>20</td> </tr> <tr> <td>P</td> <td>49/</td> <td>L</td> <td>2</td> <td>-</td> <td>2</td> </tr> <tr> <td>P</td> <td>51/</td> <td>L</td> <td>27</td> <td>-</td> <td>57</td> </tr> <tr> <td>P</td> <td>52/</td> <td>L</td> <td>5</td> <td>-</td> <td>10</td> </tr> <tr> <td>P</td> <td>55/</td> <td>L</td> <td>7</td> <td>-</td> <td>13</td> </tr> </table> <p> Assessment_of_Health_Risk_-_studies.pdf</p>	P	47/	L	13	-	16	P	49/	L	2	-	20	P	49/	L	2	-	2	P	51/	L	27	-	57	P	52/	L	5	-	10	P	55/	L	7	-	13	See the reply to comment 67.
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P	52/	L	5	-	10																																			
P	55/	L	7	-	13																																			

67	Ciprian Boboi,Asociatia Industriei de Vaping Industry Association),Romania	6.5 Assessment of Health Risks	<p>Line #</p> <p>P 47; L 13 - 16</p> <p>The Committee reports that some users experience irritation and cough, citing Polosa (2011). In fact, this study is careful to point out that these minor AEs "decreased substantially" by week 24.</p> <p>From week 4 to 24 the occurrence of minor AEs decreased in every reported measure: throat irritation (23.4 to 14.8%); mouth irritation (20.6 to 7.4%); dry cough (32.4 to 11.1%). Most importantly, there were zero serious Adverse Events reported in Polosa et al. Polosa and colleagues also draw attention to the fact that side effects most commonly reported in trials for drugs for nicotine dependence are totally absent.</p> <p>P 49; L 2 - 20</p> <p>All of the citations are in vitro studies in which there was no combustible cigarette control and which used EC aerosol exposure that wasn't relevant to human use. This led Li Volti et al (2018) (*1) to say of such studies:</p> <p>"The present study does not replicate normal conditions of use and lacks standardized protocols for E-cigarette aerosol exposure and dosimetry. To this regard, animal studies and in vitro systems often include chronic, high-dose exposures and do not approximate the type of exposure from human vaping, thus leading to extreme overestimation of toxicological effects"</p> <p>P 49; L 2 - 2-</p> <p>Again, the review here fails to consider the health impact on smokers with chronic lung conditions. As Polosa (2016) (*2), in a study of COPD patients who smoke, found:"A marked reduction in cigarette consumption was observed in ECs users. A significant reduction in COPD exacerbations was reported in the COPD EC user group, their mean (\pmSD) decreasing from 2.3 (\pm1) at baseline to 1.8 (\pm1; $p = 0.002$) and 1.4 (\pm0.9; $p < 0.001$) at F/up1 and F/up2 respectively. A significant reduction in COPD exacerbations was also observed in ECs users who also smoked conventional cigarettes (i.e. 'dual users'). COPD symptoms and ability to perform</p>	<p>As regards Polosa, see the reply to the comment 59.</p> <p>The assessment of health risks was based on the evaluation of review papers that used human data as well as in vitro studies. We agree with Li Volti et al (2018) about the use of animal and in vitro studies, but the literature searched and discussed in the Opinion mainly includes human studies.</p> <p>Please see table 1, answer 1. It is correct that in vitro studies do not perfectly represent human in vivo situation, but are a valid tool to study hazard.</p> <p>Please see table 1, answer 1.</p>
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physical activities improved statistically in the EC group at both visits, with no change in the control group.”

P 51; L 27 - 57

Current evidence unequivocally demonstrates that the air concentrations of potential toxicants are far below various internationally accepted thresholds after unrestricted vaping in closed rooms; and, of course, significantly lower than that emitted from cigarettes. We attach six papers that the Committee should consider and believe that this section should be revised in line with the evidence.

McAuley, T. R et al (2012) (*3)

O’Connell, G. et al (2015) (*4)

Logue, J. M. et al (2017) (*5)

Liu, J. et al (2017) (*6)

van Drooge, B. L. et al (2019) (*7)

Schober, W. et al (2019) (*8)

Shearston et al (2019) is not evidence that ECs cause secondhand exposure; it is a protocol for a study that has not yet reported any findings.

P 52; L 5 - 10

Diez-Izquierdo (2018) is a review in which the only in-home (natural setting) test showed no significant differences in nicotine levels on surfaces in the homes of ENDS users compared to non-smokers/non-ENDS users.

P 55, L 7 - 13

SCHEER states that the "weight of evidence concerning effects of second-hand exposure of children and adolescents cannot be established as there exists a complete paucity of evidence regarding the acute and long-term effects on cardiovascular and other health outcomes in this group."

While true, the same statement would apply to the vapor of heated cooking pots or the odor of perfume. This is because there is no rationale for investigating the effects of emissions lacking significant amounts of potentially harmful substances on health outcomes. This context and perspective are important when framing the lack of evidence.

See also sections on Exposure assessment and Risk assessment.

Ref:
 * 1- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5889678/>
 * 2- <https://respiratory-research.biomedcentral.com/articles/10.1186/s12931-016-0481-x>
 * 3- <https://pubmed.ncbi.nlm.nih.gov/23033998/>
 * 4- [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454944/-](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4454944/)
 * 5- <https://pubmed.ncbi.nlm.nih.gov/28766331/>
 * 6- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5615506/>* 7- van Drooge, B. L. et al (2019)
 * 7- <https://link.springer.com/article/10.1007/s11356-018-3975-x>
 * 8- <https://pubmed.ncbi.nlm.nih.gov/30685192/>

68	Proaño Gómez Isabel, European Federation of Allergy and Airways Diseases Patients' Associations, Belgium	6.5 Assessment of Health Risks	<p>Regarding the assessment of scientific evidence linking e-cigarettes use and health effects, we are worried that lung disease and respiratory health in general health have been side-lined (page 49) as compared to the amount of evidence collected for other diseases such as cardiovascular (pages 47-48). There is solid evidence linking e-cigarettes use with negative respiratory health outcomes, including reduced lung function (Brozek, 2019) and airway inflammation () . The evidence below responds to the Terms of reference of this SCHEER opinion: “human data on health impacts on users of electronic cigarettes from epidemiological studies or clinical 20 trials” (page 11, lines 29-31). o short-term vapor inhalation from e-cigarettes is associated with a greater prevalence of inflammation among asthma patients (Lappas, 2018) , cough and sore throat (T<S. sikrika) , and increase in airway resistance and in the slope of phase III, and a decrease in airway conductance (Gennimata, 2012) o e-cigarettes trigger processes that drive the development of the disease among COPD patients (Traboulsi, 2020) , and reduce antiviral responses among patients (Higham, 2018) o e-cigarette use might cause allergic contact dermatitis (Tzortzi 2020) and increases the risk of allergic rhinitis and asthma (Chung 2020)</p>
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Please see Table 1, answer 10.

Almost all studies mentioned above note the pressing need for research on the long-term use of e-cigarettes and its health outcomes, a call that EFA fully supports. While developing this body of evidence will take several years to be conclusive, we think that the association of e-cigarettes with adverse effects on respiratory health in the short term is already robust enough and should be fully embedded into the decision-making of the EU

institutions, firstly in this SCHEER opinion, and secondly in the EU regulatory approach to smoking and tobacco control.

Ref:

Ghosh et al (2019). Effect of Vaping on Airway Barrier Function: A Pilot Study. *European Respiratory Journal* 2019 54: PA2395; DOI: 10.1183/13993003.congress-2019.PA2395.

Traboulsi et al. (2020). Inhalation Toxicology of Vaping Products and Implications for Pulmonary Health. *Int. J. Mol. Sci.* 2020, 21, 3495; doi:10.3390/ijms21103495
European Respiratory Society Annual Congress 2012.

Lappas et al (2018). Short-term respiratory effects of e-cigarettes in healthy individuals and smokers with asthma. *Respirology* (2018) 23, 291–297 doi: 10.1111/resp.13180

69 Erkkila Brian, Foudation for a Smoke-Free World, United States of America 6.5 Assessment of Health Risks While it is true that the constituents present in aerosols could be responsible for any potential health effects from electronic cigarettes, rigorous assessments must also take into account evaluations of biomarkers. The US FDA has emphasized the importance of biomarker data in evaluating exposures and potential harms of nicotine products. (Chang 2017, 2017). In Wave 1 of the FDA's PATH study, De Jesus et al (De Jesus, 2020), Wang et al (Wang, 2019), and Xia et al (Xia 2020) measured the urinary biomarkers of daily e-cigarette users and found that the urinary concentrations of polycyclic aromatic hydrocarbons (PAHs) and tobacco-specific nitrosamines (TSNAs) – including NNAL, NNN, NAT, and NAB – were close to those of overall non-users, a group that included both former users and never users. In a 2017 study, several biomarkers were measured in urine and saliva samples from subjects who smoked electronic cigarettes, and they were similar to those of exclusive nicotine replacement therapy users and significantly below those of cigarette smokers. Similarly, in the context of evaluating electronic cigarettes the criteria for biomarker of potential harm evaluation laid out by the U.S. Institute of Medicine in Clearing the Smoke (IOM, 2001) and Modified Risk Tobacco Products (IOM, 2012), and are based upon the Hill Criteria. These biomarkers could serve as more intermediate endpoints for assessing the potential health risks of new tobacco products in the absence of long-term evidence (IOM, 2012).



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Thank you for this comment. While in general it is true that biomarkers can provide useful information on exposure and risk, in this case all available studies use biomarker levels in a comparative way. The studies do not allow a stand-alone risk estimation for e-cigarette users.

70	No agreement to disclose personal data	6.5 Assessment of Health Risks	see uploaded file below	Please see the reply to comment 71.
71	No agreement to disclose personal data	6.5 Assessment of Health Risks	<p>page 47, line 17 Impairment of the innate immunity system</p> <p>The innate immunity system forms the first line of defense against biotic and abiotic agents. An essential feature of the system is the equilibrium of reactive oxidant species (ROS) and antioxidants. Exposure to e-cig aerosol has been shown to shift the redox balance and elicit oxidative stress in cultured cells (Lerner et al. 2015b, Anderson et al., 2016, Putzhammer et al., 2016, Lee et al. 2019, Scott et al. 2018) and in animals (Lerner et al. 2015, Kaisar et al. 2017, Larcombe et al. 2017, Espinoza-Derout et al. 2019). E-cigarettes also induced oxidative stress in humans after short-term exposure (Chatterjee et al. 2019), as well as in clinical trials (Moheimani et al. 2017, Chaumont et al. 2018). In a number of human studies, the degree of oxidative stress has been compared between e-cigarette users and combustible cigarette smokers. This pertains to the biomarkers of ROS production, such as increase in 8-isoprostane, the nonenzymatic peroxidation of arachidonic acid (Carnevale et al. 2016, Biondi-Zoccai et al. 2019, Sakamaki-Ching et al. 2020), malondialdehyde formation, a measure of lipid peroxidation (Ikonomides et al. 2018), oxidative stress response proteins (Reidel et al. 2018), and suppression of the antioxidant vitamin E (Biondi-Zoccai et al. 2019). In all these comparative human studies, the potency of e-cigarettes was at least 50% ^that of combustible cigarettes.</p> <p>Exhaled nitrogen monoxide (eNO) is thought to be an indicator of inflammation in lung. The primal report on the decrease in eNO caused by e-cigarette exposure (Vardavas et al. 2012) has repeatedly been confirmed (Marini et al. (2014), Lappas et al. (2018), and Brozek et al. (2019). The extent of eNO decrease by e-cigarette exceeded 50% that caused by combustible cigarettes following short-term (Marini et al. 2014) and long-term exposure (Brozek et al. 2019).</p> <p>The observations on inflammation are less conclusive. Exposure to e-cigarettes did not elicit an overt inflammation in lung of mice (Larcombe et al. 2017, Madison et al. 2019) and humans (Song et. al. 2020a, Reidel et al. 2018). Similarly, the levels of proinflammatory cytokines such as IL-6, IL-17A, IL-1α, IL-12p40, and TNFα were not elevated upon exposure to e-cigarettes in animals (Larcombe et al. 2017, Madison et al. 2019). Exposure of mice to e-cigarette aerosol caused a small, not statistically significant increase in total cell and macrophage counts in BAL, but significantly increased the levels of MCP-1, a potent macrophage</p>	<p>A few general remarks</p> <ul style="list-style-type: none"> - Please see table 1, answer 1 - Please see table 1, answer 2 - Please see table 1, answer 3 <p>- The commnts are all on text in section 6.5.4 Human evidence for health impacts of electronic cigarettes – the comments are often refereeing to valid studies, but based on animal studies.</p> <p>The Moheimani- study has been excluded from the Opinion.</p> <p>In the section ‘Lung diseass’ p 50 the study of Vardavas is discussed.</p> <p>Thank you for the comment and the mechanistic / critical review of the literature.</p>

chemotactic cytokine, and IL-6 a modulator of number of immune-inflammatory pathways (Lerner et al. 2015). E-cigarette exposure also increased the level of circulating pro-inflammatory proteins in mice (Crotty et al. 2018).

Similar to animal studies, human studies on the impact of e-cig use on inflammation are inconsistent. Following exposure for \geq three months, e-cigarettes did not cause an increase in IL-1 β (Tsai et al. 2019). However, use of e-cigarettes for at least two years was associated with a substantial increase in IL-1 β , IL-2, IL-8, and IFN- γ (Song et al. 2020a). There was also an increase in inflammatory cytokine expression in the serum of e-cigarette users (Lee et al. 2019), a moderate increase in neutrophils in sputum and BAL (Reidel et al. 2018), and macrophages in BAL (Tsai et al. 2019, Song et al. 2020a). In a preliminary study, e-cigarette use promoted the release of apoptosis-associated speck-like protein (ASC) from inflammasomes which are crucial for immunosurveillance and clearance of pathogens (Tsai et al. 2019). Similarly, an upregulation of the ASC gene was observed by Lee et al. (2020) along with other genes implicated in inflammasomes such as CXCL1, CXCL2, and NOD2, and, in addition, an increase in pro-inflammatory cytokines (Lee et al. 2020). E-cigarette use uniquely alters the airway innate immune response to biotic and abiotic agents by causing an increase in the release of neutrophil extracellular trap-associated proteins including neutrophil elastase and myeloperoxidase (Reidel et al. 2018).

Suppression of immune functions may also play an important role in the impairment of innate immunity. E-cigarette use reduced the expression of numerous immune-related genes in human nasal scrape biopsies including genes for the expression of cytokines/chemokines, adhesion molecules, proteases, and autophagy (Martin et al. 2016). E-cigarettes decreased induced NO production and endothelial NO synthase (eNOS) to the same extent as combustible cigarettes (Fetterman et al. 2020).

E-cigarettes caused phagocytic dysfunction altering the expression of phagocytic recognition receptors and cytokine secretion pathways in cultured macrophages (Ween et al. 2017). Condensate of e-cigarette aerosol at a sublethal concentration significantly inhibited bacterial phagocytosis in alveolar macrophages freshly isolated from non-smokers (Scott et al. 2018). Exposure of mice to e-cigarette aerosol reduced phagocytosis by alveolar macrophages contributing to defective bacterial clearance (Sussan et al. 2015). In view of these observations it is plausible that e-cigarettes impair the response to infectious agents.

Several studies have shown that e-cigarettes increase in the susceptibility of human cells to viral and bacterial infection. E-cigarette aerosol promoted human rhinovirus infection in primary airway epithelial cells (Wu et al

Thank you for the comment and the mechanistic / critical review of the literature.

Thank you for the comment and the mechanistic / critical review of the literature.

2014), increased the virulence of colonizing bacteria in established cell lines of keratinocytes (HaCaTs; CLS) and lung alveolar type II cells (A549) (Hwang et al. 2016), reduced the antiviral response to poly I:C in COPD bronchial epithelial cells (Higham et al. 2016), and enhanced pneumococcal adherence to A549 cells and freshly isolated nasal epithelial cells (Miyashita et al. 2018). E-cigarette aerosol also impaired the pulmonary defense against bacterial and viral infection in various mouse models. Following intranasal infection with *Streptococcus pneumoniae*, exposure to e-cigarette aerosol increased lung viral titers and enhanced virus-induced illness and mortality (Sussan et al. 2015). E-cigarette aerosol increased nasopharyngeal pneumococcal colonisation (Miyashitca et al. 2018). Furthermore, e-cigarette exposed animals infected with influenza A virus rapidly lost augmented weight and recovered more slowly from the burden of lung inflammatory cells, edema, and hemorrhage (Madison et al. 2019). Impairment of the innate immune system may be judged an underlying factor in the etiology of cardiovascular, respiratory disease as well as cancer caused by e-cigarettes.

page 47, line 47 to be added (Franzen et al. 2018, Ikonomidis et al. 2018, Ip et al. 2020)

page 48, line 14 Exposure to e-cigarette aerosol caused endothelial dysfunction in vitro (Schweitzer et al. 2015, Putzhammer et al. 2016, Anderson et al. 2016, Barber et al. 2017, Lee et al. 2019) and in humans (Chaumont et al. 2018, Chatterjee et al. 2019, Antoniewicz et al. 2019, Biondi-Zoccai et al. 2019). In a first preliminary report, it was shown that long term exposure to e-cigarettes induces atherosclerotic lesions in mice (Espinoza-Detroux et al. 2019).

page 48, line 1 to be added (Franzen et al. 2018, Ikonomidis et al. 2018).

page 48, line 16 and endothelial particles (Staudt et al. 2018). The later effect was not found by Kerr et al. (2019).

page 48, line 17 Exposure to e-cigarettes aggravated wound healing in rats (Rau et al. 2017, Troiano et al. 2019) and delayed reconstitution of damaged brain tissue in mice (Kaisar et al., 2017) indicating a malfunction of small blood vessels. E-cigarette use caused an increase in aggregation and activation of platelets (Nocella et al. 2018), circulating platelet microparticles (Kerr et al. 2019), and NOX2-derived peptide (Carnevale et al. 2016, Biondi-Zoccai et al. 2019) which responds to activation of platelets and thrombosis. Exposure to e-cigarette aerosol reduced the anti-coagulant factor thrombomodulin in mice (Kaisar et al. 2017). These detrimental effects on blood coagulation are likely to contribute to the development of myocardial infarction and stroke.

page 48, line 40 Studies comparing the adverse impact of e-cigarettes and combustible cigarettes on the cardiovascular system show that e-cigarettes were at least 50% as potent as combustible cigarettes (Rau et al. 2017, Franzen et al. 2018, Nocella et al. 2018, Ikonomidis et al. 2018, Biondi-Zoccai et al. 2019, Kerr et al. 2019, Troiano et al. 2019, Ip et al. 2020) underlining the high toxic potential of e-cigarettes to the cardiovascular system.

Some of the effects of e-cigarettes are solely dependent on the presence of nicotine in the liquids. Thus, e-cigs without nicotine failed to affect hemodynamics as well as arterial stiffness (Franzen et al. 2018), electrocardiogram indices of ventricular polarization (Ip et al. 2020), and elastase release from neutrophils (Ghosh et al. 2019). In contrast, there are many studies indicating that e-cig aerosol free of nicotine can elicit pathophysiological changes in vitro and in vivo (Wu et al. 2014, Lerner et al. 2015, Shen et al. 2016, Scott et al. 2018, Staudt et al. 2018, Chaumont et al. 2018, Caporale et al. 2019, Wang et al. 2019, Song et al. 2020b). In some human studies, e-cig aerosol without nicotine was even more effective than aerosol with nicotine (Madison et al. 2019, Larcombe et al. 2017, Ikonomidis et al. 2018, Marini et al. 2014, Wang et al. 2019) even approaching the effectiveness of combustible cigarette smoke (Marini et al. 2014, Larcombe et al. 2017, Moses et al. 2017, Ghosh et al. 2018, Ikonomidis et al. 2018, Madison et al. 2019).

page 49, line 23A number of studies reported that e-cigarettes induce DNA strand breaks and DNA fragmentation in cell cultures (Anderson et al. 2016, Yu et al. 2016, Welz et al. 2016, Muthumalage et al. 2019) and in peripheral blood cells in rats (Canistro et al. 2017). E-cigarettes increased the incidence of 8-hydroxy-2'-deoxyguanosine DNA lesions, one of the most frequent and most mutagenic oxidative DNA lesions, in cultured cells (Ganapathy et al. 2017), and in vivo in blood cells of animals (Canistro et al. 2017). They caused a nitrosamine-dependent increase in mutagenic O6-methyldeoxyguanosines and γ -hydroxy-1,N2-propano-deoxyguanosines in lung, bladder, and heart of mice (Lee et al. 2018). In addition, exposure of mice to e-cigarettes increased the number of apurinic/apyrimidinic sites, another manifestation of DNA damage (Espinoza-Derout et al. 2019). DNA damage by e-cigarettes has also been observed in humans. Thus, e-cigarettes use increased the level of oxidative DNA damage in non-smokers (Sakamaki-Ching et al. 2020). E-cigarettes reduced the activity of DNA repair in cell cultures (Ganapathy et al. 2017), and in lung, heart, and bladder of mice (Lee et al. 2018). E-cigarettes of the Heat-not-burn-type caused significant epithelial hyperplasia and metaplasia in nasal, laryngeal, and tracheal regions in rats. In the sensitive nose region, the incidences of

Thank you for the comment and the mechanistic / critical review of the literature.

Thank you for the comment and the mechanistic / critical review of the literature.

these pathological changes did not differ between HNB and combustible cigarettes (Wong et al. 2016). E-cigarettes induced also bladder urothelial hyperplasia and lung adenocarcinoma in mice (Tang et al. 2019). Taken together, e-cigarettes are genotoxic and mutagenic in vitro and in vivo, they elicit metaplasia in various tissues and cause the development of tumors.

Thank you for the comment and the mechanistic / critical review of the literature.

page 49, line 33 A few studies have shown that e-cigarettes impair basic metabolic functions. Thus, e-cigarettes disrupted lipid homeostasis in lung in mice (Madison et al. 2019). Exposure of mice to e-cigarette aerosol decreased brain glucose uptake under normoxic and ischemic conditions and down regulated the expression of GLUT1 and GLUT3 (Sifat et al. 2018), the most abundant brain glucose transporters (Vannucci et al. 1997, Shah et al. 2012), potentially increasing the risk of ischemic brain injury and stroke. E-cigarettes impaired autophagy in murine lung (Shivalingappa et al. 2016) ultimately leading to the induction of apoptosis and cellular senescence. E-cigarettes may also impair the consistence and structure of connective tissue. Exposure of mice to e-cigarette aerosol for 3-6 months increased circulating profibrotic proteins, altered gene expression activating profibrotic pathways and increased fibrosis in kidneys, heart, and liver (Crotty et al. 2018). In rats, e-cigarette aerosol increased collagen deposition to more than 50% of the impact of combustible cigarettes (Wawryk-Gawda et al. 2020).

Thank you for the comment and the mechanistic / critical review of the literature.

page 50, line 24 Health effects of secondhand e-cigarette aerosol
Presently, there is very little evidence on the health effects of secondhand exposure to e-cigarette aerosol. Tzortzi et al. (2018) conducted a cross-over study on 40 healthy nonsmokers aged 18–35 years. They observed that a 30-minute passive exposure to e-cigarette aerosol caused an immediate alteration in respiratory mechanics and exhaled biomarkers, expressed as increased resonant frequency (fres) and reduced eNO. In a study with students aged 11-17 years with asthma, secondhand exposure to e-cigarette aerosol was associated with higher odds of reporting an asthma attack in the past 12 months (aOR, 1.27; 95% CI, 1.11-1.47 (Bayly et al. 2019).



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72	No agreement to disclose personal data	6.5.1 Consumer behaviour related to exposure assessment	Page 27 Line 43-44: The Opinion should clarify that the ISO international standard for routine e-cigarette aerosol generation was published in 2018 [(ISO 20768:2018(en) Vapour products — Routine analytical vaping machine — Definitions and standard conditions)] and it should highlight which cited studies in the	The aim of section 6.5.1 was to review available evidence on e-cigaretet use behaviour by humans, in order to inform the section on exposure assessment. For the ISO method, the aim is not not to simulate actual consumer behaviour, but to create emissions in a standardised way, for regulatory purposes. The SCHEER added a statement on standardising protocols in sections 6.5.2.
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73	Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.5.1 Consumer behaviour related to exposure assessment	Opinion actually conform to this international standard (rather than deviate, using dubious and unrealistic vaping machine parameters in e-cigarette characterisation studies).	P. 26 1. 47	We believe the references to the below studies should be added.	Generally, for Section 6.5.1, we would like to highlight the omission of data coming from EU. A recent survey from France (Chyderiotis 2019) concluded that - despite ample experimentation with vaping by adolescents - few use it regularly and its current use is frequently associated with daily smoking. Another study, covering young adults and based on data from the multicenter international study YUPESS, provides prevalence data from Central and Eastern Europe (including Slovakia, Lithuania, and Poland) (Brożek 2019). Also, a 2019 UK fact sheet (ASH UK 2019) on youth vaping acknowledged that “while some young people, particularly those who have tried smoking, experiment with e-cigarettes, regular use remains low.”	With regard to using US-data: See Table 1, answers 8 and 11.
				P. 25-26	We suggest deleting all references to ever use from Section 6.5.1. When measuring prevalence, ever use is an indicator that typically includes experimental trials and does not bring information on whether regular use is established, hence it is not relevant to exposure assessment.		

Ref.:
 ASH 2019. Use of e-cigarettes among young people in Great Britain
 ASH 2020. Use of e-cigarettes (vapes) among adults in Great Britain
 McNeill 2020 Vaping in England - an evidence update including mental health and pregnancy
 Chyderiotis 2019 Usages de la cigarette électronique en France-17 ans
 Brozek 2019 The Prevalence of Cigarette and E-cigarette Smoking Among Students in Central and Eastern Europe—Results of the YUPESS Study

74 O'Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy

6.5.1 Consumer behaviour related to exposure assessment

P26L7-8 The prevalence of adult ENDS use in the EU has been relatively stable from 2017 to 2019. Seven countries had an increase of 0.2% or less, and 3 countries had no increase in the past two years. Only two countries had a rise of 1%. See Euromonitor Database.

Please see the reply to comment 73.

P26L6-25 Ever-use data is problematic for exposure assessment. The 2016 European Regulatory Science on Tobacco (EUREST-PLUS ITC, N=1178) found that among adult ever-users in Germany, Greece, Hungary, Poland, Romania, Spain, 38.1% had used 1-2 times and 21.2% had used 3-10 times. Furthermore 85% of ever-users were no longer using ENDS (Kyriakos et al., 2018). Therefore the 6 statements based on ever-use among adults should be viewed with caution.

Current use by adults “includes many individuals who can be expected to discontinue use within 1 year” as those reporting use 5 or less times a month discontinue use frequently (Amato et al., 2017, p. e92).

A substantial number of EU adults use non-nicotine liquids. A 2016 survey of French young adults (19-22 years old) current ENDS users, 61 of 98 used only non-nicotine ENDS and an additional 19 reported using both (Kinouani et al. 2017). A 2016 face-to-face interview project with 600 daily adult ENDS users in Barcelona, Spain, 33.7% of users quitting smoking and 43.6% of users reducing cigarette use did not use nicotine liquids (Bunch et al., 2018). A 2016 online survey of current ENDS users in Poland (N=1142), 9.8% started ENDS use because they could use non-nicotine liquids (Lewek et al., 2018).

P26, L27-42 Ever-use data on youth users is problematic for exposure assessment “as ever use can include using an e-cigarette once across the lifetime, the extent of increased nicotine exposure as a result of ever e-cigarette use is unclear” (Greenhill et al. 2016, p. 616). Data from the Global Youth Tobacco Survey shows that 27% - 55% of EU youth tried ENDS on only one occasion.

Country GYTS Year % ever-users tried only one Bulgaria 2015 42.6%; Croatia 2016 36.9%; Finland 2012 *51.7%; Malta 2017 40.0%; Poland 2016 27.2%; Romania 2017 55.1%; Slovenia 2017 42.3%; * once or twice

The ESPAD@Italia 2017 survey found that over 70% of youth (15-19 years old) ever-users had used 1-9 times (Cerrai et al., 2020).

Ever-use measurement captures a substantial number of youth ENDS experimenters who do not go on to become regular users (Walker, M. et al., 2020). This is evidenced in a four year longitudinal (2015-2019) qualitative study (50 semi-structured group and 175 individual interviews) in Norway of youth aged 13-17 (Tokle, 2020). As youth became older, ENDS use became viewed as a childish practice that they discarded.

Therefore the 6 statements on youth ever-user exposure assessment should be viewed with caution. Current youth use defined as any use in the past 30 days includes a substantial number who use on only one or two days.

Country GYTS Survey Year % past month use of 1-2 days Bulgaria 2015 51.6%; Croatia 2016 61.6%; Czech 2016 46.2%; Finland 2012 *61.8%; Italy 2018 59.2%; Latvia 2014 58.3%; Malta 2017 47.0%
Poland 2016 42.2%; Romania 2017 55.9%; Slovakia 2016 56.1%;
* less than once a week

Many youth ENDS ever-users used non-nicotine products. In Finland: 52% of boys and 48% of girls, plus nicotine use declined from 2013 to 2019 (Finland Adolescent Health and Lifestyle Survey 2019). In France: 42.2% of ever-smokers and 92.9% of non-

smokers (Stenger 2016). In Italy: 72.0% overall, 31.7% used both nicotine and non-nicotine, 40.3% used only non-nicotine (GYTS 2018). In Sweden: 38% (Geidne 2016). A 2-year longitudinal study in Finland found that exclusive use of non-nicotine ENDS did not increase the risk of becoming a daily smoker compared to never ENDS users (Kinnunen 2019)

References:

Amato, M. S., Boyle, R. G., & Levy, D. (2017). E-cigarette use 1 year later in a population-based prospective cohort. *Tobacco Control*, 26(e2), e92-e96.

Bunch, K., Fu, M., Ballbè, M., Matilla-Santader, N., Lidón-Moyano, C., Martín-Sánchez, J. C., ... & Martínez-Sánchez, J. M. (2018). Motivation and main flavour of use, use with nicotine and dual use of electronic cigarettes in Barcelona, Spain: a cross-sectional study. *BMJ open*, 8(3).

Cerrai, S., Potente, R., Gorini, G., Gallus, S., & Molinaro, S. (2020). What is the face of new nicotine users? 2012–2018 e-cigarettes and tobacco use among young students in Italy. *International Journal of Drug Policy*, 86, 102941. Supplementary material.

Geidne, S., Beckman, L., Edvardsson, I., & Huldin, J. (2016). Prevalence and risk factors of electronic cigarette use among adolescents: Data from four Swedish municipalities. *Nordic Studies on Alcohol and Drugs*, 33(3), 225-240.

Kinnunen, J. M., Ollila, H., Minkkinen, J., Lindfors, P. L., Timberlake, D. S., & Rimpelä, A. H. (2019). Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: a longitudinal study among Finnish adolescents. *Drug and Alcohol Dependence*, 201, 182-187.

Kinouani, S., Pereira, E., & Tzourio, C. (2017). Electronic cigarette use in students and its relation with tobacco-smoking: a cross-sectional analysis of the I-Share study. *International Journal of Environmental Research and Public Health*, 14(11), 1345.

Kyriakos, C. N., Filippidis, F. T., Hitchman, S., Girvalaki, C., Tzavara, C., Demjén, T., ... & Zatoński, M. (2018). Characteristics and correlates of electronic cigarette product attributes and undesirable events during e-cigarette use in six countries of the EUREST-PLUS ITC Europe Surveys. *Tobacco Induced Diseases*, 16.

Lewek, P., Woźniak, B., Maludzińska, P., & Śmigielski, J. (2018). Polish e-cigarettes: users reasons to start vaping—a survey of 1142 Polish vapers. *Family Medicine & Primary Care Review*, (3), 232-235.

Tokle, R. (2020). ‘Vaping and fidget-spinners’: A qualitative, longitudinal study of e-cigarettes in adolescence. *International Journal of Drug Policy*, 82, 102791.

Walker, M. W., Navarro, M. A., Pepper, J. K., Eggers, M. E., Nonnemaker, J. M., Kim, A. E., ... & Baum, L. (2020). An Investigation of Definitions of Experimental Vaping among Youth. *Tobacco Regulatory Science*, 6(4), 289-301

75 Compernelle
Thomas, British
American
6.5.1 Consumer
behaviour related
to exposure
assessment

This section of the review is problematic as the weight of evidence (WoE) derived for e-cigarette use topography insufficiently considers inconsistencies between the studies, while the consideration of frequency of use fails to take account of prevalence data on cigarette use.

The SCHEER acknowledges that there is a large variation in use topography and this is consistently shown across studies. Consistency does not mean the absence of variation.

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The SCHEER Opinion established an overall WoE of “moderate to strong,” thereby implying that e-cigarette use topography evidence is either “medium” or “high.” However, the methodology for determining the WoE applied by SCHEER outlines that the highest weight of evidence that can be attained with “low” consistency is “moderate” (1). Thus, a low level of consistency between the studies, as seen here, would never merit a grade of “moderate to strong.”

The body of evidence on e-cigarette use topography is evidently heterogenous. In addition to variations in terms for average puff number, average puff duration, average inter-puff interval, and average puff volume being noted, the Opinion acknowledges, “a diversity in test subjects, test products, and test methods.” For example, comparing two studies in a systematic review cited in the Opinion reveals important differences in test subjects (2-4). In Strasser et al., participants were only included if they were current daily cigarette smokers and excluded for using other tobacco products, including e-cigarettes (4); conversely, in Behar et al., experienced e-cigarette users were recruited (2). Thus, the body of evidence includes e-cigarette use topography from e-cigarette naïve participants and experienced e-cigarette users. Although these critical differences are noted in the Opinion, these differences are not considered when determining consistency in the body of evidence, and the corresponding overall WoE. Critically, none of the studies were performed with standardized, validated topography equipment, which could also contribute to the varied data. Studies have shown that aerosol condensation, deposition and accurate measurements are key considerations for accurate topography equipment measurements (5-6).

Second, the comparison of e-cigarette and cigarette smoking is not consistently applied. Although the Opinion discusses e-cigarette users compared to cigarette smokers in terms of e-cigarette users taking longer puffs and having longer use sessions compared to cigarette smokers, within the section on frequency of e-cigarette use in youth, there are no data presented regarding cigarette smoking frequency. The implication of the frequency section appears to be that e-cigarette use is rising in youth and young adults. However,

SCHEER do not address similar trends for cigarette use among youth, where a decrease in prevalence is observed (7). Considering consumer trends for both products is important as the inverse relationship in use frequency between e-cigarettes and cigarettes could potentially mean that respondents predisposed to smoking cigarettes are being redirected to a potentially less harmful product. Estimates and assumptions used to model potential exposures must likewise consider cigarette trends to account for the risk and benefit balance between e-cigarettes and cigarettes.

In conclusion, SCHEER fail to adequately assess the WoE among studies with inconsistent design, methods, unvalidated topography equipment and measurements. SCHEER inadequately synthesises the body of evidence with a weight of “moderate to strong,” despite the methodology applied for appraising the WoE allowing only for a maximum grade of “moderate” for evidence of low consistency. Additionally, inconsistently referencing cigarette use behaviors calls into question the assumptions and estimates that could be used in subsequent assessments of exposures. We therefore request SCHEER to re-evaluate their approach.

Ref:

Proykova A, Kraetke R, Bertollini R, Borges T, Duarte-Davidson R, Panagiotakos D, et al. Memorandum on weight of evidence and uncertainties. Revision. 2018.

Behar RZ, Hua M, Talbot P. Puffing topography and nicotine intake of electronic cigarette users. *PloS one*. 2015;10(2):e0117222.

DeVito EE, Krishnan-Sarin S. E-cigarettes: impact of e-liquid components and device characteristics on nicotine exposure. *Current neuropharmacology*. 2018;16(4):438-59.

Strasser AA, Souprontchouk V, Kaufmann A, Blazekovic S, Leone F, Benowitz NL, et al. Nicotine replacement, topography, and smoking phenotypes of e-cigarettes. *Tobacco regulatory science*. 2016;2(4):352-62.

Spindle, T. R., Breland, A. B., Karaoghlanian, N. V., Shihadeh, A. L. & Eissenberg, T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. *Nic. Tob. Res.* 17, 142–149 (2015).

Cunningham A, Slayford S, Vas C, Gee J, Costigan S, Prasad K. Development, validation and application of a device to measure e-cigarette users' puffing topography. *Sci Rep*. 2016;6:35071. Published 2016 Oct 10. doi:10.1038/srep35071

			Levy DT, Warner KE, Cummings KM, Hammond D, Kuo C, Fong GT, et al. Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check. <i>Tobacco control</i> . 2019;28(6):629-35.	
76	Sebrie Ernesto, Campaign for Tobacco-Free Kids, United States of America	6.5.1 Consumer behaviour related to exposure assessment	<p>Use in young populations, children and adolescents (LINES 27-47) E-cigarette Use Among Middle and High School Students — United States, 2020</p> <p>This section as currently written does not cite the latest youth prevalence data from the US. We suggest including the following paper that provides the latest National Youth Tobacco Survey figures.</p> <p>Citation: Wang, TW, et al., “E-Cigarette Use Among Middle and High School Students – United States, 2020,” <i>MMWR ePub</i>, September 9, 2020.</p> <p>Trends in E-Cigarette, Cigarette Cigar, and Smokeless Tobacco Use Among US Adolescent Cohorts, 2014-2018</p> <p>This study finds that youth in the US are initiating use at younger and younger ages. This paper’s time frame, 2014 – 2018, coincides with the dramatic rise in e-cigarette prevalence, as well as the rise in popularity of JUUL in the US.</p> <p>Citation: Evans-Polce, R, et al., “Trends in E-Cigarette, Cigarette Cigar, and Smokeless Tobacco Use Among US Adolescent Cohorts, 2014-2018,” <i>American Journal of Public Health</i>, 110(2): 163-165, 2020</p> <p>Trends in Adolescent Vaping, 2017-2019</p> <p>This letter to the editor reports data from the 2017, 2018 and 2019 Monitoring the Future studies in the US, as well as the prevalence of daily e-cigarette use in 2019, a key indicator of addiction.</p> <p>Citation: Miech, R, et al., “Trends in Adolescent Vaping, 2017-2019,” <i>New England Journal of Medicine</i>, published online September 18, 2019</p> <p>Global Youth Tobacco Surveys</p> <p>The report does not include any data from the Global Youth Tobacco Surveys (GYTS). We suggest including data from three European countries that have conducted two GYTS in which</p>	Please see the Table 1, answer 11.

respondents were asked about e-cigarette use. All three countries show increases in current e-cigarette use among youth (age 13-15.)

- o In Romania, current e-cigarette use among 13-15 year-olds rose from 6.7% (8.8% boys, 4.5% girls) in 2013 to 8.2% (10.1% boys, 5.9% girls) in 2017.
- o In Georgia, current e-cigarette use among 13-15 year-olds rose from 5.7% (7.4% boys, 4.0% girls) in 2013 to 13.2% (17.3% boys, 7.7% girls) in 2017.
- o In Italy, current e-cigarette use among 13-15 year-olds rose from 8.4% (11.0% boys, 5.9% girls) in 2014 to 17.5% (21.9% boys, 12.8% girls) in 2018.

Ref:

Miech (2019). Trends in Adolescent Vaping, 2017–2019

Wang, T.W., Neff, L.J., Park-Lee, E., Ren, C., Cullen, K.A., and King, B.A. (2020). E-cigarette Use Among Middle and High School Students - United States, 2020.

Evans-Polce (2020). Trends in E-Cigarette, Cigarette, Cigar, and Smokeless Tobacco Use Among US Adolescent Cohorts, 2014–2018.

GYTS (Global Youth Tobacco Survey) Fact Sheet. Georgia 2014

GYTS (Global Youth Tobacco Survey) Fact Sheet. Georgia 2017

GYTS (Global Youth Tobacco Survey) Fact Sheet. Italy 2014

GYTS (Global Youth Tobacco Survey) Fact Sheet. Italy 2018

GYTS (Global Youth Tobacco Survey) Fact Sheet. Romania 2013

GYTS (Global Youth Tobacco Survey) Fact Sheet. Romania 2017

77	Farsalinos Konstantinos, University of Patras, Greece	6.5.1 Consumer behaviour related to exposure assessment	<p>Lines 27-47.</p> <p>The section related to the use of e-cigarettes in young populations, fails to discuss about important parameters of use. One-time or experimental use of an e-cigarette is extremely unlikely to increase any individual’s risk for developing any disease. Rather, assessment of the public health impact of e-cigarette use in youth is meaningful when data on the prevalence of three characteristics of e-cigarette use are considered: frequency of e-cigarette use, the nicotine concentration of e-cigarettes used, and the smoking status of the e-cigarette user [1]. While surveys do indeed show youth rates of ever e-cigarette use have increased considerably in recent years, they also show that youth rates of frequent use of an e-cigarette, which is more strongly indicative of a behavior likely to be sustained, and so, more strongly associated with health outcomes, have remained very low between 2011 and 2015. Data from the 2015 NYTS reveal that, while 11.1% of US youth reported having used an e-cigarette at least once in the past 30 days (i.e. current users) only 1.7% has used an e-cigarette on at least 20 of</p>
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Please see the Table 1, answer 11.

the past 30 days (i.e. frequent users) [2]. More importantly, only 0.3% of never-smoking youth reported using e-cigarettes for at least 20 of the past 30 days, with only 0.2% using them daily [2]. In 2018 and 2019, 0.44% and 1.38% of never-smoking youth reported using e-cigarettes frequently [3].

Another issue that can create confusion relevant to the use of e-cigarettes as reported in US population surveys is the use of these devices to inhale marijuana. This has been a recent trend in the US, and a recent study showed that up to almost 70% of e-cigarette users have ever used marijuana in an e-cigarette [3]. Unfortunately the survey only examined ever marijuana use; thus, it is not possible to determine what proportion of participants may be using e-cigarettes predominantly or exclusively for marijuana use. Results from the Monitoring the Future Study, another school-based national survey in the US, though, indicate that there is substantial overlap among use of marijuana, cigarettes and e-cigarettes [4].

In conclusion, the authors of the Scheer report failed to specify the frequency of e-cigarette use and the smoking status of e-cigarette users among youth, factors that are critical in examining the impact of e-cigarettes in this population subgroup. The fact that frequent and daily e-cigarette use is by far lower in never-smokers and is largely confined to ever-smokers have important public health implications and might even show that e-cigarettes could act as a distraction from smoking.

1. Polosa R, Russell C, Nitzkin J, Farsalinos KE. A critique of the US Surgeon General's conclusions regarding e-cigarette use among youth and young adults in the United States of America. *Harm Reduct J.* 2017 Sep 6;14(1):61. doi: 10.1186/s12954-017-0187-5.
2. Farsalinos K, Tomaselli V, Polosa R. Frequency of Use and Smoking Status of U.S. Adolescent E-Cigarette Users in 2015. *Am J Prev Med.* 2018 Jun;54(6):814-820. doi: 10.1016/j.amepre.2018.03.003.
3. Farsalinos K, Barbouni A, Niaura R. Changes from 2017 to 2018 in e-cigarette use and in ever marijuana use with e-cigarettes among US adolescents: analysis of the National Youth Tobacco Survey. *Addiction.* 2020 Jun 13. doi: 10.1111/add.15162.
4. Evans-Polce RJ, Veliz PT, Boyd CJ, McCabe SE. E-Cigarette and Cigarette Use Among U.S. Adolescents: Longitudinal Associations With Marijuana Use and Perceptions. *Am J Prev Med.* 2020;58(6):854-857. doi:10.1016/j.amepre.2020.01.013.

78 Olteanu Vlad,vlad.olteanu@juul.com,Belgium 6.5.1 Consumer behaviour related to exposure assessment

Frequency of use of electronic cigarettes SCHEER uses data in this section from the Special Eurobarometer 458 dated 31 May 2017(field work performed in March 2017). This data is outdated and should be supported by more recent data on smoking prevalence and electronic cigarette use. In particular, an “e-cigarette evidence review, undertaken by leading independent tobacco experts” published by Public Health England (2018); a 2020 study (Kapan et al.) in the International Journal of Environmental Research and Public Health, entitled “Use of Electronic Cigarettes in European Populations:A Narrative Review” or specific Member State studies such as 2019 study(Pinkas et al.) International Journal of Environmental Research and Public Health entitled: “The Prevalence of Tobacco and E-Cigarette Use in Poland: A 2019 Nationwide Cross-Sectional Survey”. SCHEER (lines 21 to 23) finds that “Both former (aOR 7.49, 95%C.I. 6.51 to 8.61) and current tobacco smokers (aOR 22.88, 95%C.I: 20.16 to 25.97) were more likely to have ever tried electronic cigarettes than never smokers.” We failed to see the application that SCHEER should have made of this finding in the relevant sections 6.6 and 6.7 (role in initiation, respectively role in cessation and dual use). 27 Use in young populations, children and adolescents. Underage people should not use or have access to electronic cigarettes or any products that contain nicotine. Underage use of ENDS products is detrimental to harm reduction and JUUL Labs is committed to preventing underage access to its electronic cigarette products.We recommend that SCHEER uses data gathered under this heading extremely prudently. The data referenced was collected between 2013 and 2017, during which time (and since), the evolution of the e-cigarette industry was significant, as was the evolution of relevant regulation. For instance, until May 2016, the specific rules of the Tobacco Products Directive(TPD) 2 were not fully enforced within the European Union and the previous TPD did not contain specific rules on electronic cigarettes. In light of this, devices currently available to consumers, their design features and specific characteristics, should be properly analysed and categorised and should only include data post relevant regulation (post May 2016). SCHEER notes at line 37 that “the proportion of youth who reported ever using electronic cigarettes varies substantially across surveys.” That

Please see the Table 1, answer 11.

finding alone requires the highest prudence when inferences, conclusions and/or policy recommendations based on such large data spread are drawn. 49 Smoker protocols –how a specific user uses an electronic cigarette, smoking behaviour. Puff topography is, indeed, an important measure of how consumers use e-vapour products. SCHEER selected only two studies that analyse puff topography. To ensure that conclusions made are valid, other studies freely available on the National Library of Medicine website (<https://pubmed.ncbi.nlm.nih.gov/30053435/>) should be included in the SCHEER opinion. In particular, the study of Vansickel et al. “Characterization of puff topography of a prototype electronic cigarette in adult exclusive cigarette smokers and adult exclusive electronic cigarette users” and the study of Farsalinos et al. “Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation” should be thoroughly reviewed. Quoted studies were uploaded with this submission as either a full .pdf or as a first page .jpg as allowed by the 1MB file limit or copyright rules.

Ref:

Eurobarometer 458. Attitudes of Europeans towards tobacco and electronic cigarettes. March 2017

Farsalinos (2013). Evaluation of Electronic Cigarette Use (Vaping) Topography and Estimation of Liquid Consumption: Implications for Research Protocol Standards Definition and for Public Health Authorities' Regulation

GOV.UK (2018). PHE publishes independent expert e-cigarettes evidence review. Press release Feb 2018

Kapan (2020). Use of Electronic Cigarettes in European Populations: A Narrative Review. *Int. J. Environ. Res. Public Health* 2020, 17, 1971; doi:10.3390/ijerph17061971

Pinkas (2020). The Prevalence of Tobacco and E-Cigarette Use in Poland: A 2019 Nationwide Cross-Sectional Survey. *Int. J. Environ. Res. Public Health* 2019, 16, 4820; doi:10.3390/ijerph16234820

Vansickel (2018). Characterization of puff topography of a prototype electronic cigarette in adult exclusive cigarette smokers and adult exclusive electronic cigarette users. *Regul Toxicol Pharmacol* 2018 Oct;98:250-256. doi: 10.1016/j.yrtph.2018.07.019. Epub 2018 Jul 24.

Much more than 2 studies were included, as described in the text, and elaborated in the supplementary A3.1 and A3.2, including the ones mentioned in the comments (Vansickel; Farsalinos). In total, 19 studies have been described.

79	Sproga Maris, Smoke Free Association of	6.5.1 Consumer behaviour related to exposure assessment	page 26, lines 27-47 Again - many publications used by the SCHEER reflect the situation in the United States and the report does not contain later data from the EU and the UK. A number of EU studies demonstrate low e-cigarette use amongst
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Please see the Table 1, answers 8 and 11.

	Latvia,Lat via		<p>young people. It is also important to distinguish between regular use and ever use, these are the trials that do not equal with regular use. Therefore, ever use should not be the basis for the exposure assessment and should not be used as a reference on pages 25 and 26.</p> <p>Ref: Brozek 2019 The Prevalence of Cigarette and E-cigarette Smoking Among Students in Central and Eastern Europe—Results of the YUPESS Study. doi: 10.3390/ijerph16132297 Chyderiotis 2019 Usages de la cigarette électronique en France à 17 ans : résultats de l'enquête nationale ESCAPAD 2017. https://doi.org/10.1016/j.bulcan.2019.06.016</p>	
80	Vuerich Michela,A NEC,Belgi um	6.5.1 Consumer behaviour related to exposure assessment	<p>Page 27, lines 1-45: To facilitate risk assessment of ingredients of e-liquids evaporated it may be also useful to determine the daily consumption of e-liquids in those cases where systemic long-term effects are assessed based on a daily dose. According to various sources this volume can even exceed 10 ml per day. In this case it does not matter that much what frequencies, number of puffs etc. precisely are (i.e. whether somebody takes 600 puffs à 50 ml per day in 10 hours or 300 puffs à 100 ml in 5 hours. Of course, this is not relevant for concentration related effects such as short-term local irritation.</p>	<p>Thank you for this suggestion. SCHEER decided not to use this additional approach in the risk assessment because 1) concentration data in liquides could not be retrieved for all substances considered relevant (Section 6.5.2.3) 2) this approach does not honour the exposure scenario for e-cigarette users for which a daily dose is a poor approximate value (Section 6.5.5.2). 3) Some substances are produced by the heating the liquid and related to the device and are not directly related to liquid composition.</p>
81	Olteanu Vlad,Juul Labs Inc. ,Belgium	6.5.1 Consumer behaviour related to exposure assessment	<p>SCHEER uses data in this section from the Special Eurobarometer 458 dated 31 May 2017 (field work performed in March 2017). This data is outdated and should be supported by more recent data on smoking prevalence and electronic cigarette use. In particular, an “e-cigarette evidence review, undertaken by leading independent tobacco experts” published by Public Health England (2018); a 2020 study (Kapan et al.) in the International Journal of Environmental Research and Public Health, entitled “Use of Electronic Cigarettes in European Populations: A Narrative Review” or specific Member State studies such as 2019 study (Pinkas et al.) International Journal of Environmental Research and Public Health entitled: “The Prevalence of Tobacco and E-Cigarette Use in Poland: A 2019 Nationwide Cross-Sectional Survey”. SCHEER (lines 21 to 23) finds that “Both former (aOR 7.49, 95%C.I. 6.51 to 8.61) and current tobacco smokers (aOR 22.88, 95%C.I: 20.16 to 25.97) were more likely to have ever tried electronic cigarettes than never smokers.” We failed to see the</p>	<p>Please see reply to comment 78.</p>

application that SCHEER should have made of this finding in the relevant sections 6.6 and 6.7 (role in initiation, respectively role in cessation and dual use). 27 Use in young populations, children and adolescents Underage people should not use or have access to electronic cigarettes or any products that contain nicotine. Underage use of ENDS products is detrimental to harm reduction and JUUL Labs is committed to preventing underage access to its electronic cigarette products. We recommend that SCHEER uses data gathered under this heading extremely prudently. The data referenced was collected between 2013 and 2017, during which time (and since), the evolution of the e-cigarette industry was significant, as was the evolution of relevant regulation. For instance, until May 2016, the specific rules of the Tobacco Products Directive (TPD) 2 were not fully enforced within the European Union and the previous TPD did not contain specific rules on electronic cigarettes. In light of this, devices currently available to consumers, their design features and specific characteristics, should be properly analysed and categorised and should only include data post relevant regulation (post May 2016). SCHEER notes at line 37 that “the proportion of youth who reported ever using electronic cigarettes varies substantially across surveys.” That finding alone requires the highest prudence when inferences, conclusions and/or policy recommendations based on such large data spread are drawn. 49 Smoker protocols –how a specific user uses an electronic cigarette, smoking behaviour Puff topography is, indeed, an important measure of how consumers use e-vapour products. SCHEER selected only two studies that analyse puff topography. To ensure that conclusions made are valid, other studies freely available on the National Library of Medicine website (<https://pubmed.ncbi.nlm.nih.gov/30053435/>) should be included in the SCHEER opinion. In particular, the study of Vansickel et al. “Characterization of puff topography of a prototype electronic cigarette in adult exclusive cigarette smokers and adult exclusive electronic cigarette users” and the study of Farsalinos et al. “Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation” should be thoroughly reviewed. Quoted studies were uploaded with this submission as

			either a full .pdf or as a first page .jpg as allowed by the 1MB file limit or copyright rules.	
82	Woessner Julie, International Network of Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.5.1 Consumer behaviour related to exposure assessment	<p>Page 26 / Lines 1-2 and Lines 49-50 Using “Smoker protocols” and “smoking behaviour” is misleading. It doesn’t respect SCHEER’s own terminology as defined on page 19.</p> <p>Page 26, lines 27-47 This section exclusively reports US data, and we question why no EU data is included. SCHEER recognize in the Summary (p. 7, lines 38-42) that many of the published studies in the Preliminary Opinion deal with US data and set forth why conclusions drawn from US data may not be directly transferable to the EU. SCHEER then states that because trends may “spill over” into the EU, “developments outside the EU should not be disregarded.” We respectfully note, however, that this section 6.5.1 does not merely consider US data, it does so at the complete exclusion of EU data. Given the substantial differences in the US and EU markets, due in no small part to vastly different regulatory environments, we believe that the US data in this and many other sections should be largely discarded.</p> <p>Leaving aside the issue of whether US data should be included in this section (to the exclusion of EU data) and without considering the weight (if any) to be given to it, we note that more recent data from the 2020 National Youth Tobacco Survey (NYTS) in the US reports a marked decline in youth use of e-cigarettes. For example, among high school students, last 30-day use is down from 27.5% in 2019 to 19.6 percent 2020, and self-reported use of e-cigarettes likewise decreased among middle school students in that same time period, from 1.24 million in 2019 to 550,000 in 2020. Examining e-cigarette use in a population without also considering data on smoking for that population provides an incomplete picture. For example, the 2019 NYTS reports a decline in cigarette smoking among youth, the lowest ever reported by the NYTS. An estimated 5.8% of high school students and 2.3% of middle school students reported current cigarette smoking in 2019.</p>	<p>The SCHEER agrees with this comment, and changed the wording, when referring to e-cigarette use behaviour or protocols.</p> <p>Please see the Table 1, answer 8.</p>
			Page 26 / Line 53	

Using “electronic cigarette smoking behaviour” is misleading. It doesn’t respect SCHEER’s own terminology as defined on page 19.

Page 26, lines 29-31
 The reference to Schulenberg et al., 2017 (which corresponds with the reference SCHULENBERG JE, JOHNSTON LD., O’MALLEY PM, BACMAN JG, MIECH R, PATRICK ME. 2016 Volume II: College students & adults ages 19-55. 2017 at p. 88, lines 7-8 in the Reference Section) does not appear to be accurate. We believe the correct reference for Page 26, lines 29-31 would be to Volume I of that work.

Page 27 / Line 43
 Using “smoking protocol” is misleading, “usage protocol” would be better to respect SCHEER’s own terminology as defined on page 19.

Ref:
 Wang et al (2019). Tobacco product use and associated factors among middle and high school students—United States, 2019. MMWR Surveillance Summaries, 68(12), 1.

83	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO)	6.5.1 Consumer behaviour related to exposure assessment	<p>Page 26, lines 27-47</p> <p>The data presented includes only “ever use” and “use in the past 30 days.” Neither of these measures informs on patterns of use that would differentiate between one-time or limited experimentation versus regular use. We believe reporting that includes data on “frequent use” (at least 20 of the last 30 days and not simply at least one in the last 30 days or ever use) is necessary for a better understanding of the use of e-cigarettes in various populations.</p> <p>Ref: Villanti et al. (2017). Original investigation Frequency of Youth E-Cigarette and Tobacco Use Patterns in the United States: Measurement Precision Is Critical to Inform Public Health. doi:10.1093/ntr/ntw388</p>	Please refer to Table 1, answer 11.
84	Brose Leonie, King's College London, United Kingdom	6.5.1 Consumer behaviour related to exposure assessment	<p>Page 26, lines 27-47 “Use in young populations, children and adolescents”</p> <p>None of the references provided in this section use data from Europe, it is entirely based on data from the US with very limited applicability to the EU. This section is in contrast to the summary and section 3 which both use different figures for youth prevalence, including some from the EU.</p>	Please see the Table 1, answer 11.

Importantly, this section highlights some of the weaknesses of the literature search and evidence synthesis. Including US data may have some merit; however, it should be the most recent data available, whereas this section reports data from 2013 to 2016. Later data have been available for a substantial amount of time and it is unclear why the authors of this section in the opinion rely entirely on data that are years out of date, even allowing for the unusually long lag between the end date of their search and publication. This raises serious questions about the reliability of the evidence that the SCHEER preliminary opinion more widely is based on. To give examples for just 16 lines of text on this one page (as only one attachment is possible, only the first reference is attached):

1. page 26, lines 28-31: “The 2015 National Youth Tobacco Survey (NYTS) in the US reported that 27.1% of middle and high school students ever used electronic cigarettes. Rates of ever use were similar in the 2016 survey, ranging from 17.5% among 8th grade students to 29.0% among 10th graders, and 33.8% among high school seniors”. More recent data including past 30-day use instead of solely ever use have been published multiple times, for example by Cullen et al., 2019. Data from the surveys are also regularly published by the CDC, e.g for 2020: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6937e1.htm>

2. page 26, lines 31-34: “The most recent youth rates reported from the PATH survey (Wave 1 in 2013–2014) indicate much lower rates of ever use, with only 10.7 percent of youth ages 12 to 17 reporting ever using an electronic cigarette even once or twice (Backinger, 2017).” These are not at all the most recent data or publications for youth rates using PATH data. Publications available in 2019 include for example Stanton et al., 2019 reporting on Wave 2.

3. Page 26, lines 34-36: “Conversely, rates in the 2015 35 YRBS are substantially higher, with 44.9 percent of high school students reporting ever 36 using “electronic aerosol products”. Again, data from the surveys in 2017 and 2019 have been published.

4. Page 26, lines 42-44: refers to MTF data for 2016. As with all the other surveys in this section, more recent data had been published multiple times by 2019 for example by Miech et al. 2019.

Ref:

Cullen et al (2019). E-Cigarette Use Among Youth in the United States, 2019. JAMA. 2019;322(21):2095-2103. doi:10.1001/jama.2019.18387

85	No agreement to disclose personal data	6.5.1 Consumer behaviour related to exposure assessment	<p>p.26, 147: SCHEER only considers US data, which is a totally different market from the European one, mainly because of different regulation. Furthermore, data provided are not up to date. The most recent NYTS data (2020) show that the number of young people using electronic cigarettes fell down by about 1.8 million (doc. 11). Moreover, comparative studies examining the US and European Countries confirm that relying on US data is not a rational way to examine the prevalence in Europe. For instance, Hammond et al (2020) undertook a study analysing the rates of vaping and smoking among 16- to 19-year-olds in the US, Canada and England from 2017 to 2019 (doc. 12).</p> <p>Ref: Wang et al (2020). E-cigarette Use Among Middle and High School Students — United States, 2020. MMWR September 18, 2020, Vol. 69, No. 37 Hammond et al (2020). Changes in Prevalence of Vaping Among Youths in the United States, Canada, and England from 2017 to 2019 DOI: 10.1001/jamapediatrics.2020.0901</p>	Please see the Table 1, answers 8 and 11.
86	Ciprian Boboi,Asociatia Industriei de Vaping (Vaping Industry Association),Romania	6.5.1 Consumer behaviour related to exposure assessment	<p>P 26/ L 27 – 47</p>  <p>Consumer_behaviour_related_to_exposure_</p>	Please see the Table 1, answers 8 and 11.
87	Ciprian Boboi,Asociatia Industriei de Vaping (Vaping Industry Association)	6.5.1 Consumer behaviour related to exposure assessment	<p>Line # P 26; L 27 - 47</p> <p>Only data from the United States - where the market is regulated in an entirely different way - are provided. Moreover, the data provided is not up to date. The most recent (2020) NYTS data (https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey) showed that 1.8 million fewer young people use e-cigarettes. Youth smoking rates in the US are at record lows.</p>	Please see the Table 1, answers 8 and 11.

	n),Romani a		<p>Comparative studies looking at the US and European countries confirm that reliance on data from the US is not a rational way to look at prevalence in Europe. Hammond et al (2020) (https://jamanetwork.com/journals/jamapediatrics/article-abstract/2765159) undertook a cohort study examining rates of vaping and smoking among youths aged 16 to 19 years in the United States, Canada, and England from 2017 to 2019.</p> <p>The study shows that smoking prevalence among UK youth and young adults decreased even further from 2018 to 2019, even as vaping prevalence slightly increased.</p> <p>Again, the report fails to consider what has happened to youth smoking rates during this period, continuing in its error of failing to take account of cigarettes in the discussion around e-cigarettes.</p>	
88	Zvi Herzig,UB I,USA	6.5.1 Consumer behaviour related to exposure assessment	<p>Regarding the gateway effect, the report misquotes Levy et al. A time trend 37 analyses on national representative data on electronic cigarette and tobacco use in the US 38 by Levy et al. (2019) noted a decline in past 30-day smoking prevalence between 2014- 39 2017, which coincides with the timeframe of electronic cigarette proliferation in the US, 40 however the authors noted that while there has been a decrease in smoking rates during 41 the past years in the US, this could also be attributable to the influence of other tobacco 42 control interventions.</p> <p>Levy et al, however conclude that analyses suggest that tobacco control policies are at most responsible for a small part of the accelerated reductions in youth and adult smoking [during the vaping era]. https://tobaccocontrol.bmj.com/content/28/6/629</p>	Please see the Table 1, answer 5.
89	Spina Francesco, Private,Italy	6.5.2 Exposure assessment	<p>Page 39 lines 11 to 24 Conclusions on second-hand exposure it seems there is a deliberate will to not include the attached Burstin Sutdy published in 2014, where it concludes: The vast majority of predicted exposures are <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was plausible.</p>	This comment relates to the risk assessment for second-hand exposure in section 6.5.5.6. With regard to using data prior to 2015: see Table 1, Answer 2. In that way the non-inclusion of the Burstyn study is, indeed, “deliberate”. Secondly, Hess et al. (2016) provide a systematic review involving 16 studies. This study used quality control criteria whereas Burstyn et al. explicitly state “ no explicit quality control criteria were applied in selection of literature for examination. Thirdly, TLVs relate to exposure of workers, not to exposure of the general population. Finally, the risk assessment is predominantly based on several lines

					of evidence including the exposure assessment for second-hand exposure, hazard identification and hazard assessment,
90	No agreement to disclose personal data	6.5.2 Exposure assessment	pag. 33, line 12-23	In the assessment of nicotine concentration in the aerosol of e-cig, the opinion does not take into account the results of the study by Pacifici R et al. 2015, which showed that the switch to electronic smoking does not generate an increase in the nicotine consumption in non-dual electronic smokers. Such an evidence is important and should be considered particularly in high cardiovascular risk smokers: the absence of combustion (and the consequent significant lower exposure to its toxicants) is a net and high advantage as the combustion products are mostly responsible for the cardiovascular harm and not the nicotine. Pacifici R, Pichini S, Graziano S, Pellegrini M, Massaro G, Beatrice F. Successful nicotine intake in medical assisted use of E-cigarettes: a pilot study. Int. J. Envir. Research Public Health 2015; 12:7638–7646. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4515680/pdf/ijerph-12-07638.pdf .	With regard to the comparison with smoking: see Table 1, Answer 1. In addition, the SCHEER argues that ‘most of the cardiovascular effects demonstrated in humans are consistent with the known sympathomimetic effects of nicotine’(Section 6.5.4), opposing the view that combustion products are mostly responsible.
91	Mayer Bernhard-Michael, University of Graz, Pharmacology & Toxicology, Austria	6.5.2 Exposure assessment	page 31, line 30	This statement is misleading. Inhaled vapor constituents are almost entirely retained in the body, including 95 % of the nicotine [1].	SCHEER agrees. The sentence is modified in “Harmful components are partially exhaled by users of electronic cigarettes”.
			page 37, lines 9-12 and page 38, line 14 - page 38, line 24	SCHEER refers to questionable estimates based on exhaled breath (Visser et al. 2014, 2015, 2019) instead of discussing published quantitative analyses of indoor air quality after vaping in closed rooms. Exceptions are an early paper by Schober et al. (2014) and the study by Geiss et al. (2016), which both show that the levels of potentially harmful compounds are far below the accepted thresholds for indoor air. Unfortunately, the committee ignored all other published studies relevant for second-hand exposure, showing that the concentrations of potentially harmful substances in room air is very low after unrestricted vaping, and no reason for concern [2-6].	Unfortunately, the comment does not make clear why the estimates from the controlled studies are questionable. The comment seems to include both exposure to users and second-hand exposure. Only for the latter, indoor air quality studies are considered relevant.
			page 41, lines 51-57	Concerning the claimed effects of menthol, see my reply to section 6.5.3.	With regard to literature selection for second-hand exposure: see Table 1, Answer 2. Besides Schober (2013) and Geiss (2016), also PAH-levels measured by van Drooge were included in section 6.5.2.2. Hess included the McAuley and O’Connell papers. Thank you for citing the additional papers of Liu et al. (2017) and Schober et al. (2019). These papers are now considered , though this did l not change the conclusion.
				Due to the upload limit, only 4 out of 6 cited papers are attached (#1-3, #4 and #6). 1. St.Helen et al. Addiction 111, 535-544 (2016)	

2. McAuley et al. *Inhal. Toxicol.* 24, 850-857 (2012)
3. O'Connell et al. *Int. J. Environ. Res. Public Health* 12, 4889-4907 (2015)
4. Liu et al. *Int. J. Environ. Res. Public Health* 14, 969 (2017)
5. van Drooge et al. *Environ. Sci. Pollut. Res.* 26, 4654-4666 (2019)
6. Schober et al. *Int. J. Hyg. Environ. Health* 222, 486-493 (2019)

Ref:

Gideon (2015) Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes

McAuley (2012) Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality

O'Connell (2015) An Assessment of Indoor Air Quality before, during and after Unrestricted Use of E-Cigarettes in a Small Room

Schober (2019) Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars

92 Dawkins
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United
Kingdom

6.5.2 Exposure
assessment

Section 6.5.2.3 Quantification of aerosol concentrations. In particular, page 33, lines 4-10. Page 38, lines 10-12.

The section on aldehydes on page 33 covers studies that have used a smoking machine specifically to measure aldehydes. Our work (Kosmider et al., 2018) directly looked at exposure to formaldehyde, acetaldehyde, acetone and acrolein but it is not included in this section. It is important to include this study as the report states that "...the majority of exposure studies do not control for the generation of dry puffs, particularly in studies using variable power devices, which could result in testing conditions and reported carbonyl levels that have no clinical relevance or context" and concludes that "studies with controlled realistic conditions are rare." (page 35, lines 4-10). Our 2018 study is one of the very few studies that DID use realistic puffing conditions as we programmed the smoking machine to mimic real puffing patterns collected from e-cigarette users in the lab. In our later paper (Kosmider et al., 2020, *Scientific Reports*) we went even further and used puffing topography data collected from participants over a 4 week period outside of the lab to program the smoking machine to measure 14 aldehydes and keytones. We found that use of lower nicotine e-liquid concentrations increased both formaldehyde and acetaldehyde exposure in both studies. Our findings suggest, counter-intuitively, that use of higher nicotine concentrations may be safer than lower ones – a finding that has direct implications for the 20mg/mL nicotine limit in e-liquids. In our 2020 study we additionally report that using the lower nicotine concentration increased cancer potency by two to two and a half times. Compared to cigarette smoking however, these carcinogenic potentials are 3116.9 to 21818.2 times lower suggesting a huge decrease in exposure when smokers completely switch to vaping. This comparison to cigarette smoking is of utmost importance since e-cigarettes are being used predominantly by smokers in the EU, yet this comparison is lacking in this section and in the whole of section 6.5. Given the SCHEER conclusions on page 38 (lines 10-12) that "The highest uncertainty is related to the

Additional text and suggested references were added to the Opinion.

proper distinction of realistic versus dry puff conditions and the corresponding carbonyl concentrations”, our work is particularly important as it’s unlikely that our data reflect dry puff conditions since the smoking machine was programmed based on actual e-cigarette users’ puffing behaviours.

References

Kośmider, L., Kimber, C., Kurek, J., Corcoran, O., Dawkins, L. Compensatory Puffing With Lower Nicotine Concentration E-liquids Increases Carbonyl Exposure in E-cigarette Aerosols, *Nic Tob Res* 20 (8), 998-1003 (2018). <https://doi.org/10.1093/ntn/ntx162>

Kosmider, L., Cox, S., Zaciera, M., Kurek, J., Goniewicz., ML., McRobbie, H., Kimber, C. & Dawkins, L. Daily exposure to formaldehyde and acetaldehyde and potential health risk associated with use of high and low nicotine e-liquid concentrations. *Sci Rep* 10, 6546 (2020). <https://doi.org/10.1038/s41598-020-63292-1>

Note: I couldn’t upload the second scientific paper as, even after reducing the file size, it still exceeded the 1MB limit, however it can be found in full here: <https://www.nature.com/articles/s41598-020-63292-1>

93	CHampagnac maxime,Phode,France	6.5.2 Exposure assessment	<p>p32 table 3</p> <p>Diethylene glycol and tTNSA should be part of the risk assement as there are only related to products with tobaaco extracts https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p> <p>A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.</p> <p>For diethylene , Products from 2014 were produced befor the TPD implementation</p>	See Table 1, answer 4.
94	Champagnac Maxime,Phode,France	6.5.2 Exposure assessment	<p>p36 lines4 to 8 "5</p> <p>Farsalinos et al (2015) analysed TSNAs, using a second-generation device and three commercial e-liquids. No TSNAs were detected in the aerosol. Goniewicz et al. (2014) measured NNN at 0.8-4.3 ng/150 puffs and NNK at 1.1-28.3 ng/"</p> <p>STudies relized before the TPD implementation TSNAs should'nt be part of the risk assment for e-cigarette but only for those with tobbaaco extracts :https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p> <p>A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.</p>	No changes needed. See Table 1, answer 4.

95	Poirson Philippe, Sovape, France	6.5.2 Exposure assessment	<p>[p. 30 l. 36-38] The analysis of Farsalinos (2015) concerns liquids prior to TPD. An analysis of liquids in European market after TPD entry into force would have been relevant to examine the regulatory impact on health risk.</p> <p>[p. 31 l. 49] Schober (2014) presents a methodological shortcoming in the comparative measures, as explained in Farsalinos 2014. This should be underlined or the study discarded.</p> <p>[p. 31 l. 48] Report must add the nicotine exposure for bystander is reduced by more than 100 times in comparison of cigarette smoke (Martin et al. 2019) and during less times (Bertholon 2014). Scungio 2018 show “the corresponding ELCR value of mainstream EC aerosol ($6.11-7.26 \times 10^{-6}$) is 5 orders of magnitude lower than that of mainstream traditional cigarettes smoke, and also lower than the guideline values defined by EPA and WHO. Particle number concentrations equal to $6.30-9.08 \times 10^3$ part. cm^{-3} with bi-modal distribution (at 30 nm and 90 nm) and surface area concentrations of $5.16-5.90 \times 10^7$ $\text{nm}^2 \text{cm}^{-3}$ (at 300 °C), respectively, were measured in second-hand aerosol of ECs, leading to extremely low values of ELCR due to the exposure to second-hand EC aerosol ($1.24-2.70 \times 10^{-8}$)”.</p> <p>[p. 33] Flora et al. specifies studied liquids with nicotine pharma grade or not grade. TPD provides pharma grade and some of the data, in this study and maybe others referenced, cannot concern the legal European market. We also note that this study comes from the laboratories of the tobacco company Altria.</p> <p>[p. 38 l. 28] Schober (2014) has methodological problem as explained by Farsalinos (2014)</p>	<p>The SCHEER agrees, but presently it is too early for this. More data should become available.</p> <p>Indeed, the increases observed for aluminium and PAH may be questioned, since control environmental measurements were performed on a separate day. The Opinion is amended.</p> <p>No changes needed. See Table 1, answer 1.</p> <p>Scungio et al., (2018) was described in Section 6.5.5.4. They indeed show low calculated risk estimates. It is noted that study is based on a continuous exposure scenario. Nevertheless, this line of evidence indeed could have been included in the conclusion in Section 6.5.5.6. <i>This is corrected in the final Opinion.</i></p> <p>See Table 1, Answer 4. The SCHEER removed these data from the Opinion.</p> <p>The methodological problem was addressed in the Opinion.</p>
96	Champagnac maxime, Phode, France	6.5.2 Exposure assessment	<p>p37 lines 5-8 "The relevant compounds for the RA in electronic cigarette aerosols are mainly the solvent carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs), by-products of thermal decomposition of some of these constituents, notably carbonyls, and metals originating from the device." A TNSA comes only from tobacco extracts, and not from pharma</p>	<p>See Table 1, answer 4.</p>

grade nicotine, the same condition used for flavourings (if added) should be use

The relevant compounds for the RA in electronic cigarette aerosols are mainly the solvent 5carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs)(il tobacco extracts added to e-liquid) , by-products of thermal decomposition of some of these constituents, notably carbonyls, and metals originating from the device

97	Champagnac Maxime,Phode,France	6.5.2 Exposure assessment	p37 lines 9-10 "The risk assessment will be based on the aerosol concentrations found in the Visser et al 9 study (2014 and 2015). " The risk assesment shouldn't ne made with nitroamines nor diethylene Visser et Al 2014 it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." A specific risk eassesment should be done for product with Tobacco extract exposing users to TNSA	See Table 1, answer 4.
98	Champagnac Maxime,Phode,France	6.5.2 Exposure assessment	p38 lines 4-6 "In spite of the high overall variability of results, caused by unstandardized experimental settings and expressed by the large ranges reported, the quality and the consistency of the data selected is judged to be medium to high. " This statement should be revised. For carbonyl emissions in order to avoid risk of dry puff condition, the generation process should a vaping machine (not a smoking machine) as defined in the ISO 20768. Smoking machine are used with device at the horizontal devices, when vaping machin allows puffing génération with a 45° (as e-cig are used) angle reducing risks of dry puff (i.e AFNOR XP D90-300-3). E-cigarette user avoid the risk of dry puffing moving their device, wicking the coil and avoidind he bad taste of dry puffing. In the ISO interlaboratory study to validate the methode for analysing adehydes in earosol of e-cigarette, the stadnard product have to be doped with aldehyde because, the no quantifcable and reproductible aldehyde emission without dry puff. (on contrary to the heated tobacco products whiche are reproductible in aldehyde aerosol generation)	As stated in the Opinion, in the Visser et al. report dry puff conditions were avoided.
99	Champagnac maxime,Phode,France	6.5.2 Exposure assessment	p38 table 6 TNSA shouldn't be part of the general risk assesment for electronique cigarettesas Nitroamines can only comes from E-liquids containing Tobacco extracts.	Please see Table 1, answer 4.

			<p>Visser et Al 2014 it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."</p> <p>A specific risk assesment should be done for product containing tobacco extracts exposing to TNSA in aerosols.</p>	
100	Champagnac Maxime,Phode,France	6.5.2 Exposure assessment	<p>p58 Line 48 "For TSNAs MoEs are 521 and 2297 for scenario 1 and 2, respectively. A carcinogenic risk cannot be excluded for scenario 1 and is uncertain for scenario 2. 4" Shouldn be part of the analyse for second Hand exposure: Vissed et Al 2015 "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."</p> <p>Could be use only for product with tobbaoco extracts</p>	Please see Table 1, answer 4.
101	Becher Rune,Norwegian Institute of Public Health,Norway	6.5.2 Exposure assessment	<p>The preliminary opinion points out that the prevalence of ultrafine particles (UFP) is high in e-cigarette smoke/vapor, but that there is not enough evidence to assess the health effects of these. However, there is comprehensive evidence in general that UFPs may have high reactivity and solubility and some fractions may be inhaled more deeply and with varying translocations of the UFPs. Thus, mass calculation of exposure can give a misleading picture of the exposure. UFP can thus lead to e-cigarettes having more serious negative health effects. This should at least be mentioned. We also miss a more comprehensive assessment of which toxins one can be exposed to when using e-cigarettes, what happens in the e-cigarette (chemistry / temperature / oxygen supply), which substances are formed and inhaled, or at least how unpredictable this is. There are, differences both between the types of e-cigarettes (many brands, 1st-4th generation e-cigarettes, in the "life cycle" of an e-cigarette, between the types of e-cigarette liquid, different additives, etc. Evaluating "flavors" but not preservatives, thickeners (like vitamin e acetate), or dyes (for the e-liquid) also seems like it can be a serious weakness in light of recent years' experience from the US.</p>	<p>The potential exposure to UFP due to e-cig use is described in some detail on p29 lines 9-47 of the Opinion. Both size/number estimation as well as size/mass estimations are given.</p> <p>Section weight of evidence: while in general strong to moderate evidence is found concerning the increased exposure to particles due to electronic cigarette us, while nanoparticles are not taken into account due to the scarce data.</p> <p>It is clear from the attentions given to the nanoparticles in the sections describe above that thte SCHEER considers nanoparticles as potential hazardous but due to the sarce data no weight can be given – and ths no speculations can be made.</p> <p>No change in the Opinion needed.</p>
102	No agreement to disclose personal data	6.5.2 Exposure assessment	<p>Page 30 Line 27: THE OPINION IS NOT REPRESENTATIVE OF THE CURRENT POST-EUTPD MARKET</p> <p>It is important for SCHEER to note that the cited data from 2017 and 2018 may not be representative of or generalizable to the</p>	See Table 1, answer 8.

current market. The nicotine used in e-cigarettes is extracted from tobacco. Its purity, however, differs by manufacturer and grade. Responsible e-cigarette manufacturers only use pharmaceutical grade quality nicotine that complies with the EU or US Pharmacopoeia. These grades require, for example, single impurities to be less than 0.5% (5 mg/g) and total impurities to be less than 1% (10 mg/g). As for the trace levels of tobacco-specific nitrosamines (TSNAs) that may be present, these are impurities from the nicotine added to e-liquids, at levels that are negligible[1], but in compliance with EU or US Pharmacopoeia.

P 22 L20: PLEASE REFER TO OUR RESPONSE IN SECTION
6.2 (DESIGN FEATURES)

P39 L18: EXHALED E-CIGARETTE AEROSOLS DO NOT
POSE A RISK TO BYSTANDERS OR INDOOR AIR QUALITY
BASED ON CURRENT SCIENCE

See Table 1, answer 4.

E-cigarettes do not generate side-stream emissions and pose no known risk to bystanders based on current science. Scientific studies have shown indoor vaping does not release chemicals or toxins into the air at levels which would pose any air quality issue to bystanders when compared to indoor air quality standards. Studies have shown that ambient air in a room in which e-cigarettes are used fully complied with indoor air quality regulations and standards where established[2]. Moreover, the California Department of Public Health and the National Institute for Occupational Safety and Health conducted a number of air quality assessments in e-cigarette shops in Cincinnati and found that, even in a shop with relatively poor ventilation where 13 customers vaped all day, creating a visible cloud, a range of flavouring compounds and formaldehyde assessed were all below the lowest occupational exposure limits and nicotine was virtually undetectable[3].

The SCHEER disagrees: based on the limited data available risks were identified, though the weight of the evidence is at best moderate.

Risk management is not within the remit of the SCHEER.

The UK Government has also published guidance to employers in 2016 (which remains current) encouraging workplaces to adopt pro-e-cigarettes policies that make it as easy and convenient as possible for adult smokers to transition on the basis there is “currently no evidence of harm from second-hand e-cigarette

vapour”[4]. This view is shared by the UK National Health Service,[5] Cancer Research UK[6] and many others. This major Government policy guidance was omitted from the Opinion.



6.5.2_Exposure_assessment.pdf

103	Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.5.2 Exposure assessment	<p>P. 28 l. 4 to P. 30. l. 2 As correctly pointed out by the SCHEER “Electronic-cigarette aerosol is composed of droplets of e-liquids” and are therefore liquid. Nonetheless, in Section 6.5.2 the SCHEER’s Opinion wrongly uses the term “particles” in several paragraphs which implies that the aerosol is composed of solid particles. We therefore suggest to replace the word “particles” in this section with “droplets” where appropriate. This is necessary on P. 28 l. 10; l. 19, l.20, l. 47, and further on P. 29 l. 9, l. 10, l. 11, l. 12, l. 13, l. 14, l. 16, l. 18, l. 19, l. 21, l. 23, l. 24, l. 27, l. 31, l. 33, l. 49, l. 51.</p>	<p>The SCHEER introduced clarifications about the word “particles” aerosols and “droplets” where appropriate. We kept the terms as they are in the cited publications.</p>
			<p>P. 31 l. 32 It is mentioned that “Because electronic cigarettes are only active when users take a puff, electronic cigarettes do not continue to smoulder between puffs”. In fact “Continue to smoulder” erroneously implies that e-cigarettes smoulder when used. Because e-cigarettes do not produce smoke and also do not smoulder, we suggest to delete the word “continue” and change the sentence to read “Because electronic cigarettes are only active when users take a puff, electronic cigarettes do not generate an aerosol between puffs.”</p>	<p>The SCHEER agrees to delete the word “continue” and change the sentence to read “Because electronic cigarettes are only active when users take a puff, electronic cigarettes do not generate an aerosol between puffs.”</p>
104	O’Leary Renee, Center of Excellence of the Acceleration of Harm Reduction, Italy	6.5.2 Exposure assessment	<p>P36L42 A study (Wiener and Bhandari, 2020) reviewed blood lead (N=1899) and urinary cadmium, barium, and antimony (N=1302) urine test data in the 2015-2016 US National Health and Nutrition Examination Survey (NHANES). There were no significant differences in the levels of exposure to metals between participants who had never used ENDS and participants who were current or former ENDS users. The researchers conclude that ENDS are not a source of exposure to these heavy metals.</p> <p>P37L4-P38L12 Biomarker data is relevant evidence. A measurement of exposure data for 28 ENDS users who had quit smoking for a minimum of 2 months were significantly lower compared to cigarette smokers (Hecht et al., 2016). 1-HOP levels (PAH) were similar to non-</p>	<p>This study was not selected, since any exposure to metals in aerosols will hardly be detectable in blood and urine in view of significant background exposures. Therefore it is not surprising that current or former e-cigarette use failed to reach a statistical significance in the association with metals.</p> <p>With regard to comparative studies: see Table 1, answer 1.</p>

smokers. The study found significantly lower levels of metabolites for ENDS users compared to cigarette users for 1-hydroxypyrene (1-HOP, PAH), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronides (total NNAL), 3-hydroxypropylmercapturic acid (3-HPMA, acrolein), 2-hydroxypropylmercapturic acid (2-HPMA, propylene oxide), 3-hydroxy-1-methylpropylmercapturic acid (HMPMA, crotonaldehyde), and S-phenylmercapturic acid (SPMA, benzene).

A clinical study of 33 ENDS users, 4 weeks after quitting, found that the mean 3-HPMA levels (acrolein) had decreased 79% for exclusive ENDS users and 60% for dual ENDS and cigarette users (McRobbie et al., 2015).

Thank you for pointing out this study. It was, however, not selected in view of fact that it does not contribute to answering the questions in the ToR. 1

A before and after study (Goniewicz et al., 2017) tested 20 Polish adult cigarette users for biomarkers of exposure after 2 weeks, with half of the participants substituting ENDS and half continuing to smoke. Significant reductions in exposure levels were detected for many toxicants in the ENDS users.

Toxicant	Significant	Reduction	p<0.05
NNK			64%
Ethylene		oxide	61%
1,3-Butadiene			84%
Crotonaldehyde			67%
Acrolein			56%
Benzene			76%
Acrylamide			57%
Acrylonitrile			79%
Propylene		Oxide	53%
PAH		1-Hydroxyfluorene	58%
PAH		3-Hydroxyfluorene	34%

From Supplemental Table 3

The substantial and significant reduction in 1,3-butadiene is particularly noteworthy as it is assessed as the greatest source of cancer risk in tobacco smoke (Fowles and Dybing, 2003). Goniewicz et al. conclude that “e-cigarettes may effectively reduce exposure to toxic and carcinogenic substances among smokers who switched to these products” (p. 165).

Pulvers et al. (2018) conducted a 4-week observational study on 40 adult cigarette users who added or substituted ENDS use. Biomarker levels of NNAL, benzene, and acrylonitrile were significantly reduced in all participants. Participants reporting exclusive ENDS use for at least 2 weeks had in addition significant reductions in metabolite levels of ethylene oxide

and acrylamide with reductions in acrolein levels bringing them into the range of non-smokers.

While significant reductions in biomarkers of exposure are not evidence of an absence of risk, these studies (and industry studies not cited) demonstrate that exposures to toxicants are substantially and significantly lower for ENDS than in cigarettes. People who smoke can substantially reduce their exposure to known toxicants by replacing ENDS for cigarettes, even when it is not complete substitution.



6.5.2_references.pdf

105 Serafimov Lubomir, Bulgarian Vape Association of Manufacturers, Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E-liquid, Bulgaria

6.5.2 Exposure assessment

The SCHEER Opinion is overstating the evidence of secondhand vapour exposure.

It says that second-hand vapour may be a cause of cancer and cardiovascular disease in bystanders, with the evidence described as ‘weak to moderate’. There is in fact, no evidence at all that supports this statement. The associations between secondhand smoke exposure and cancer and cardiovascular disease are weak and speculative coming from extrapolations of the risk from direct active vaping (using electronic cigarette) exposure. It is not clear in what circumstance would SCHEER state “no evidence” – i.e. is there a minimum at which the risks are so small or unlikely, that it is no longer appropriate to raise them? There are three key differences in the way bystanders are exposed to secondhand vapour aerosol compared to secondhand smoke:

1. The quantity emitted. Most of the inhaled vapour is absorbed by the user and only a small fraction is exhaled (15% or less, depending on the constituent). In contrast, about four times as much environmental tobacco smoke comes directly from the burning tip of the cigarette than is exhaled by the smoker. There is no equivalent of this “sidestream smoke” for vaping(using an electronic cigarette).
2. The toxicity of the emissions. Tobacco smoke contains hundreds of toxic products of combustion that are either not present or present at very low levels in vapour aerosol. Vapour emissions do not have toxicants present at levels that pose a material risk to health. Exposure to nicotine, itself relatively benign, is unlikely to

The SCHEER disagrees with the view that there is no evidence at all. The compounds identified in exhaled air of electronic cigarette users include particulate matter, nicotine, glycerol, propylene glycol, formaldehyde and acetaldehyde, VOCs, metals and, in rare cases, PAH. It is acknowledged by SCHEER that the reported concentrations are orders of magnitude lower for all these substances than those reported for exposure of electronic cigarette users and that the weight of evidence for exposure is weak to moderate. Indeed, the risk assessment is based on direct acting exposure, since these data are considered the best available. The overall uncertainty in the conclusion is clearly expressed in the conclusions on the weight of evidence: weak to moderate. A more quantitative estimate of the risk requires more data.

reach a level of pharmacological or clinical relevance. 3. The time that the emissions remain in the atmosphere. Environmental tobacco smoke persists for far longer in the environment (about 20-40 minutes per exhalation). The vapour aerosol droplets evaporate in less than a minute and the gas phase disperses in less than 2 minutes. Therefore, to the extent that there is evidence of cancer risk, it suggests the risk is negligible. A study has found (Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers) cancer risk from e-cigarette aerosol to be vastly lower than for cigarette smoke – "...excess life cancer risk (ELCR) for second-hand smokers was five orders of magnitude (10,000 times) larger than for second-hand vapers." This information is more useful than saying the evidence for "carcinogenic risk due to cumulative exposure to nitrosamines is weak to moderate", as stated in the Opinion.

Ref: Avino P, Scungio M, Stabile L, Cortellessa G, Buonanno G, Manigrasso M. Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers. *Sci Total Environ.* 2018 Nov 15;642:137-147. doi: 10.1016/j.scitotenv.2018.06.059. Epub 2018 Jun 18. PMID: 29894873.

The reference provided was not included since Scungio provided a more specific study on e-cigarette exposure to carcinogens (2018) which was described in Section 6.5.5.4 indeed showing low calculated risk estimates. It is noted that study is based on a continuous exposure scenario. Nevertheless, this line of evidence indeed could have been included in the conclusion in Section 6.5.5.6. This is corrected in the final Opinion.

106 Waclaw Michalina, Prawo dla Ludzi (Law for People), Poland

6.5.2 Exposure assessment

Exaggerated evidence of passive exposure to fumes has been presented. It concluded that there was "low to moderate" evidence that secondhand inhalation of vaping smoke causes cancer. However, no data was actually provided. According to research, the risk that e-cigarette smoke is carcinogenic is negligible. For example, a study by Avino et al., 2018 Second-hand Aerosol From Tobacco and Electronic Cigarettes: Evaluation of the Smoker Emission Rates and Doses and Lung Cancer Risk of Passive Smokers and Vapers - found that the cancer risk from e-cigarette aerosol is significantly lower than that of cigarette smoke.

Please see the reponse to comment 105.

107 Stucki Andreas, P ETA International Science Consortium

6.5.2 Exposure assessment

Thank you to SCHEER for providing a comprehensive opinion on electronic cigarettes.

Page 28, line 53: It states that "...using exposure conditions and animal models that are relevant to real-life inhalation exposure in humans" Recommendation: Please remove "...and animal models...".

The sentence is a quote from a US-FDA-document. Apparently, US-FDA has animal models in mind and these most likely will not be rodents.

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It should be noted that there are no animal models that are relevant to real-life inhalation exposure in humans. In addition to interspecies differences, some of which were mentioned in section 6.5.3, rodents are obligate nose breathers, while exposure to electronic cigarette vapour in humans is mainly through the mouth, thereby bypassing important filtering in the nose. Furthermore, in the Opinion on Additives used in tobacco products (Opinion 2) from 2016 (https://ec.europa.eu/health/sites/health/files/scientific_committee/s/scheer/docs/scheer_o_001.pdf), the SCHEER wrote on page 5: “For ethical reasons, the performance of new animal studies is not endorsed to assess the contribution of an additive to the tobacco product toxicity. Therefore, as a principle, only in silico and in vitro studies should be considered for new testing in Step 3, following the EU policy to ban animal studies for chemicals to be used in voluntary products.” (Abstract, page 5). These sentences are also true for electronic cigarettes and animal methods should not be endorsed.

We would welcome if the SCHEER considered adding a statement discouraging the use of animals to its opinion on electronic cigarettes. The below paragraph, adapted from the tobacco additives opinion, is a suggestion for such a paragraph: For ethical reasons, the performance of new animal studies is not endorsed to assess the risk of electronic cigarettes. Therefore, as a principle, only in silico and in vitro studies should be considered for new testing, following the EU policy recommending implementation of 3R methods for refinement, reduction, and replacement of animal models, leading to the ban of animal studies for chemicals to be used in voluntary products such as cosmetics (EU Regulation no. 1223/2009). Non testing or alternative testing approaches followed for the evaluation of cosmetic ingredients, whenever relevant to electronic cigarettes, could be considered.

Page 28, lines 54+55
It states “(Recommendation 6-2 of the Food and Drug Administration and other US federal research sponsors and / or device manufacturers)”.
It is not clear what Recommendation 6-2 of the Food and Drug

SCHEER agrees and has included a remark (“it is noted by the SCHEER that EU policy bans animal studies for chemicals to be used in voluntary products”).

			Administration and other US federal research sponsors and / or device manufacturers is and suggest to clarify by adding references.	
108	Gonzalez Ureña Angel, Universidad Autónoma de Madrid, Spain	6.5.2 Exposure assessment	<p>I enjoyed reading your report. My comment in related to the 6.5.2.3 section on Quantification of aerosol concentration and, more specifically to the subsection dedicated to second hand exposure. On page 38 line 18 of the manuscript, one reads that "Data on second hand exposure are however scarce". Last year our group published a paper(see pdf attached) entitled "On the Passive Exposure to Nicotine from Traditional Cigarettes Versus e-Cigarettes" whose main conclusion was : The main conclusion of the investigation was the drastic reduction in nicotine exposure of the passive subject when the smoker of a combustion cigarette was replaced by the vaper of an e-cigarette. In all cases here analyzed, the average nicotine exposure was reduced by two orders of magnitude. For example, at a distance of 100 cm between the passive and active smoker, and adverse but sometimes realistic spatial configuration, the average nicotine exposure per puff varied from 600ng to five ng when the active subject was vaping an e-cigarette.</p> <p>Another point of relevance of the present investigation is the finding of an inverse quadratic dependence of the nicotine exposure with the distance between the passive and active smoker or vaper. These preliminary results may stimulate future investigations in our field for (short and long range) spatial modelling of toxicant diffusion in both indoor and outdoor environments.</p> <p>Ref: Martín (2019). On the Passive Exposure to Nicotine from Traditional Cigarettes Versus e-Cigarettes. International Journal of Public Health Research 2019; 7(1): 11-17 http://www.openscienceonline.com/journal/ijphr</p>	<p>Thank you.</p> <p>With regard to the comparison with smoking: see Table 1, answer 1. In the conclusions, the SCHEER acknowledges that the reported second-hand exposure levels are orders of magnitude lower for all the substances considered than those reported for exposure of electronic cigarette users and that the weight of evidence for exposure is weak to moderate. Your results seem to match the results of the Visser study in Table 6 very well. Thank you for your paper: the results have been included in Section 6.5.2.3.</p>
109	Arffman Päivi, Vapers Finland, Finland	6.5.2 Exposure assessment	<p>— 6.5.2.2 Exposure to aerosols, qualitative description (page 30, line 16 - page 31, line 27)</p> <p>— 6.5.2.3 Quantification of aerosol concentrations (page 31, line 55 - page 38, line 12) See also: — 6.5.3 Hazard identification of most relevant compounds (page 39, line 26 - page 46, line 15)</p>	<p>With regard to the comparison with smoking: see Table 1, answer 1.</p>

In the handling of this topic the level of risk from these exposures has been completely disregarded, i.e., whether the amounts of toxicants released from e-cigarettes are high or low and how they compare to exposures to toxicants from smoking. The latter information is particularly relevant given that the use of e-cigarettes is mainly concentrated among smokers/ex-smokers and the main purpose of use being smoking cessation, reduction or prevention of relapse to smoking. Studies have shown that the amount of contaminants released from e-cigarettes is small and the level of risk they represent is low. Compared to cigarette smoke, the levels of harmful substances are substantially lower. Most of the harmful substances in cigarette smoke are not present in e-cigarette aerosol at all, including combustion products, which are primarily responsible for the harmful health effects of smoking.

Ref:

Stephens, W.E. (2017). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tobacco Control, 2017

Kosmider (2020). Daily exposure to formaldehyde and acetaldehyde and potential health risk associated with use of high and low nicotine e-liquid concentrations

CRUK (2017). E-cigarettes safer than smoking says long-term study <https://www.cancerresearchuk.org/about-us/cancer-news/press-release/2017-02-06-e-cigarettes-safer-than-smoking-says-long-term-study>

Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England

110 Arffman Päivi, Vape rs Finland, Finland

6.5.2 Exposure assessment

— Second-hand exposure (page 38, line 14 - page 39, line 24)
See also:

— 6.5.4 Health effects related to second-hand exposure to aerosol from electronic cigarettes (Page 51, line 27 - page 52, line 10)

— 6.5.5.6 On risks for second-hand exposure (page 62, lines 11-43)

Due to the small amount of pollutants released into the environment from e-cigarettes, exposure to aerosols released from e-cigarettes have not been shown to pose a health risk to bystanders. In indoor measurements, pollutant levels have been below permissible limit values.

See answers to comments 105 and 108.

It should also be noted that there is no side-stream aerosol emitted from the tip of an electronic cigarette, just the exhaled aerosol

entering the atmosphere. Particles are liquid droplets that evaporate rapidly, approximately in 10–20 seconds, in comparison with the conventional cigarette particulate emissions which had a dissipation time of approximately 1.4 hours in a 35 m³ room (Lamos et al., 2019).

Ref:

Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England

Health Hazard Evaluation Report 2015-0107-3279

<https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0107-3279.pdf>

Klepeis (2017). Fine particles in homes of predominantly low-income families with children and smokers: Key physical and behavioral determinants to inform indoor-air-quality interventions

Scungio (not published). Measurements of electronic cigarette-generated particles for the evaluation of lung cancer risk of active and passive users.

Lamos (2019). Real-Time Assessment of E-Cigarettes and Conventional Cigarettes Emissions: Aerosol Size Distributions, Mass and Number Concentrations.

111 Farsalinos
Konstantinos,
University of
Patras, Greece

6.5.2 Exposure
assessment

Page 32, lines 11-20
(sub-section 6.5.2.3 Quantification of aerosol concentrations)

The authors assessed the exposure using (in most cases) emissions data reported as amount per puff (table 3, page 32 of the Scheer report). This is particularly problematic when assessing human exposure. It is well established that such reporting in e-cigarettes has major limitations when comparing devices with different power settings or puff durations [1]. It does not take into account that aerosol yield (liquid consumption) per puff increases substantially at higher power settings [2] or with higher puff durations [3]. Additionally, devices with different performance and design characteristics have highly variable aerosol and nicotine yields at the same puffing patterns [4]. Even if the thermal degradation rate (percent of liquid that is transformed to aldehydes) remains stable, the higher liquid consumption per puff will inevitably increase the absolute levels of carbonyls per puff, but not necessarily the amount per liquid consumption. Since surveys of vapers have shown that electronic cigarette use consumption is measured as liquid consumption per day rather than number of puffs [5,6], reporting the level of emissions per liquid consumption rather than puffs is essential and relevant to true exposure. In fact, all e-cigarette aerosol emissions should ideally be reported as amount per liquid

The SCHEER disagrees with the view that reporting the level of emissions per liquid consumption rather than puffs is essential and relevant to true exposure. This approach ignores the toxicokinetics and dynamics of exposure via aerosols during use of e-cigarettes as explained in Section 6.5.5.2 and may lead to an underestimation of the risk for which the actual concentration in the puff is the most relevant exposure parameter. Of course, there is high variability in these exposure estimation given the number of conditions that can change as noted in the comment.

consumption, and liquid consumption is probably the main determinant of emissions exposure. Characteristically, Kosmider et al. reported higher carbonyl exposure when using 6mg/mL compared to 24mg/mL liquid, based on puffing patterns and liquid consumption during a 1 hour session in experienced vapers [7]. However, by calculating the levels of aldehyde emissions per gram of liquid, based on the information on aerosol yield per puff, slightly higher formaldehyde (4.343 µg/g vs. 4.153 µg/g vs) and acetaldehyde (3.027 µg/g vs. 2.640 µg/g) were observed at 24mg/mL compared to 6mg/mL nicotine concentration liquid. This clearly shows that it is the higher liquid consumption at 6mg/mL that mainly determines the higher carbonyl exposure in users.

In conclusion, it is imperative to understand the consumption characteristics and measurement units when examining aerosol exposure in realistic settings. The Scheer report does not address this issue sufficiently, and this has adverse implications in the resulting risk assessment analysis.

1. Farsalinos KE, Gillman G. Carbonyl Emissions in E-cigarette Aerosol: A Systematic Review and Methodological Considerations. *Front Physiol.* 2018 Jan 11;8:1119. doi: 10.3389/fphys.2017.01119.
2. Gillman IG, Kistler KA, Stewart EW, Paolantonio AR. Effect of variable power levels on the yield of total aerosol mass and formation of aldehydes in e-cigarette aerosols. *Regul Toxicol Pharmacol.* 2016 Mar;75:58-65. doi: 10.1016/j.yrtph.2015.12.019.
3. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El Hellani A, Baalbaki R, Saliba N, Shihadeh A. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine Tob Res.* 2015 Feb;17(2):150-7. doi: 10.1093/ntr/ntu174.
4. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Protocol proposal for, and evaluation of, consistency in nicotine delivery from the liquid to the aerosol of electronic cigarettes atomizers: regulatory implications. *Addiction.* 2016 Jun;111(6):1069-76. doi: 10.1111/add.13299.
5. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *Int J Environ Res Public Health.* 2013 Dec 17;10(12):727

112 Dahlmann 6.5.2 Exposure
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P 28 - 29
SCHEER extensively discusses the number and size of particles emitted by e-cigarettes without mentioning that they are liquid droplets, like the particles in fog or the aerosol emitted by metered-dose inhalers prescribed to patients with asthma or other restrictive lung diseases.

(see similar comment above)
Details on the characteristics of the particles could be found in the preliminary Opinion on:
p.6,Line .34-38,
p.11, Line 20-28,

Alliance, Germany

In contrast to the solid particles in tobacco smoke, which cause long-term inflammatory processes in the lung, liquid droplets dissolve upon contact with tissue. Their size determines the site of deposition (oral cavity, upper airways, or lung) but is otherwise irrelevant.

SCHEER lists every substance that has ever been detected in e-liquids or aerosols, regardless of their concentrations or their impact on human health. The committee's reference to Klager et al., who reported that 60 % of tested liquids contained diacetyl or acetoin, was conducted in the United States and is not relevant to the European Union where the use of such substances is prohibited by current legislation.

Other potentially harmful compounds listed in this section are reactive oxygen species, tobacco-specific nitrosamines, and metals. The concentration of free radicals in e-cigarette aerosols is about 10-fold lower than in tobacco smoke (Bitzer et al, (2020)). Tobacco-specific nitrosamines are hardly detectable (Goniewicz et al (2014)), and the concentrations of metals are far below internationally accepted thresholds (Farsalinos et al (2018)). P 49; L 2 - 2-Again, the review here fails to consider the health impact on smokers with chronic lung conditions. As Polosa (2016), in a study of COPD patients who smoke, found:

“A marked reduction in cigarette consumption was observed in ECs users. A significant reduction in COPD exacerbations was reported in the COPD EC user group, their mean (\pm SD) decreasing from 2.3 (\pm 1) at baseline to 1.8 (\pm 1; $p = 0.002$) and 1.4 (\pm 0.9; $p < 0.001$) at F/up1 and F/up2 respectively. A significant reduction in COPD exacerbations was also observed in ECs users who also smoked conventional cigarettes (i.e. 'dual users'). COPD symptoms and ability to perform physical activities improved statistically in the EC group at both visits, with no change in the control group.”

p.27, Line 46-57.

Additional clarification has been added.

Section 6.5.2.2 indeed gives an impression of the compounds that can be encountered in aerosol inhaled by users of e-cigarettes and 6.5.2.3 an overview of quantitative levels reported. However, in the next step SCHEERs prioritizes, selecting relevant compounds for the RA in electronic cigarette aerosols in the EU: the solvent carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs), by-products of thermal decomposition of some of these constituents, notably carbonyls, and metals originating from the device. The risk assessment for this selection was subsequently based the aerosol concentrations found in the controlled studies of

With regard to TSNAa: see Table 1, Answer 4.

With regard to risks from metals, the SCHEER also concludes (though not based on “internationally accepted thresholds”), that the weight of evidence for risks from metals is weak.

With regard to comparisons with data on smokers: see Table 1, Answer 1.

P 32; L 1 - 20 No changes needed.
P 37; L 4 - 12

The data in table 3 shows only the levels of the identified substances in e-cigarette aerosol. However, this data lacks context or meaning when not read in conjunction with the requisite data for combustible cigarettes.

RIVM has collected significant data on these points, and it is surprising that this is not considered relevant.

This flaw in the Committee’s approach - comparing the risks of e-cigarettes with the risk of no use rather than with use of cigarettes - is evident in its conclusions on p37. These conclusions completely fail to identify the relative risk with cigarette smoking as a critical factor when considering its risk assessment protocol.

P 40; It is stated that 60 mg of nicotine is fatal for humans. The 60-mg estimate, which would implicate nicotine toxicity comparable to that of the deadly poison cyanide, was based on erroneous self-experiments performed in the mid of the 19th century and has been corrected to 0.5 - 1 g several years ago, as per Mayer (2014).

According to the harmonised classification and labelling approved by the European Union, nicotine is fatal if swallowed, is fatal in contact with skin, is fatal if inhaled and is toxic to aquatic life with long lasting effects. Additionally, the classification provided by companies to ECHA in REACH registrations identifies that this substance causes serious eye damage and causes skin irritation. With respect to intoxication of humans, estimates range from 60 mg from self-testing up to more recent estimates of 0.5–1 g of ingested nicotine, corresponding to an oral LD50 of 6.5–13 mg/kg from Mayer (2014). According to Mayer smoking a cigarette results in uptake of approximately 2mg of nicotine and gives rise to mean arterial plasma concentrations of about 0.03mg/L."

See also reply to comment 193.

The Opinion has been amended accordingly.

113	Vuerich Michela,A NEC, European consumer voice in	6.5.2 Exposure assessment	6.5.2.1 Aerosol characteristics Page 29, lines 1-2: The CORESTA recommendations (3.0 sec puff duration and 55 mL puff volume) are representative for 1st and 2nd e-cigarettes and, therefore, probably outdated. Puff volumes of 100 – 150 ml as indicated in the previous section seem more appropriate.	No changes needed.The lack of validated, widely available standard methods for the assessment of e-cigarette emissions results in difficulties with replicating studies and conclusions in experiments conducted by different groups on the same products (Farsalinos et al., 2018). On the other hand, in the absence of product-specific relevant testing standards, the majority of existing product
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standardisation, Belgium

assessment standards have been established at ISO level, namely for the routine analytical smoking machine specifications and puffing parameters (ISO, 2000a), the definition and procedures for assessing basic smoke parameters such as total particulate matter (TPM) (ISO, 2000b), water (ISO, 1999), nicotine (ISO, 2013), and nicotine-free dry particulate matter (NFDPM) (ISO, 2000b), frequently referred to as 'tar', as well as procedures for the quantification of other specific constituents, specifically carbon monoxide (CO) (ISO, 2007), benzo[a]pyrene (ISO, 2017a), menthol (ISO, 2012), and tobacco-specific nitrosamines (TSNAs) (ISO, 2016). For many other constituents, even though ISO standards are not currently available, standardized methodologies and inter-laboratory trial results are readily available as industry standards through the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), with a number of methods presently in development phase within the ISO technical committee in charge of tobacco and tobacco products, such as for carbonyls and volatile compounds.

It is advisable to use standardised protocols that are relevant for human exposure.

6.5.2.2 Exposure to aerosols, qualitative description
Page 30, lines 33-35: The Klager et al. (2017) study found "that diacetyl and acetoin were the most prevalent of the flavouring chemicals in electronic cigarette aerosols being found in more than 60% of samples". It is then astonishing that these substances are not included in Table 2 (most frequently used ingredients in e-liquids other than nicotine).

Page 30, lines 36-35: Diacetyl and/or acetylpropionyl were found in over 70% of sampled liquids and their aerosols (Farsalinos et al., 2015a). It is then astonishing that these substances are not included in Table 2 (most frequently used ingredients in e-liquids other than nicotine).

6.5.2.3 Quantification of aerosol concentrations
Page 37, lines 9-10: It is difficult to understand why only the Visser et al. studies (2014 and 2015) have been chosen for the risk assessment rather than the full range of available studies.

Diacetyl and acetoin are included in Tables 3,4,5.

The same as above. No changes needed.

This is explained in Section 6.5.5.2 and 6.5.5.3. The Visser studies are the only experimental studies available with controlled conditions and realistic use topography, whereas the risks are estimated using the MoE approach. Other risk assessments predominantly compare exposure levels of substances in aerosol from electronic cigarettes with health based guidance values and this approach is

<p>114 Compernelle Thomas, British American Tobacco, Belgium</p>	<p>6.5.2 Exposure assessment</p>	<p>We respectfully request SCHEER to correct and amend the following: P29, LN2-7: text appears to be standalone – it is context P29, LN10-16: clarification of particle concentration from e-cigarettes required as stated as 4×10^9 and “of the order of 10^6 to 10^7 particles/cm³. P29, LN37-42: data reported in the publication of Williams et al. (1) is based on a single product type tested in 2012/13 and as such is highly unlikely to represent more modern e-cigarette designs. More recent publications quantifying metals in e-cigarette aerosol have demonstrated metals below limits of detection, quantification and below or not statistically different to background levels and should therefore be included in the weight of evidence P30, L4-30, Margham et al. (2), Flora et al. (3), Farsalinos et al. (4), Farsalinos and Rodu (5), Tayyarah and Long (6). Data from Williams et al. (7) are relevant to P36, LN23-56. P29, LN9: the term ultrafine particles may lead to misunderstanding as they should be viewed as ultrafine droplets, explained by the short lifetime as stated in L13. Section 6.5.2.2 Data from early generation e-cigs are over-represented in comparison to their current level of use by consumers. Section 6.5.2.3 depends heavily upon the data of Visser et al. The cited RIVM reports do not seem to address the potential background chemical contribution to levels reported in aerosols (2) and may overestimate results. P30, LN24 & P37, LN6: ethylene glycol is listed as a solvent carrier, however, this is not listed as an ingredient in e-liquids within the EU, as stated in Appendix 2 of the report.</p>	<p>considered less suitable since these ignore the toxicokinetics and dynamic of e-cigarette vaping as explained in Section 6.5.5.2. The SCHEER has rephrased the Opinion accordingly. Supplementary references proofing the inserted data, p.28. The suggested references are included in the opinion, in the citation Zhao, 2020, p.36, l.42. No changes needed. See above, reply to comment 103. The cited RIVM reports has been deleted Ethylene glycol is listed as a solvent carrier, has been included as an ingredient in e-liquids within the EU, as stated in Appendix 2 of the report.</p>
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P30, LN25 & P37, LN6-7: TSNAs are listed as an impurity of nicotine, whilst P36, LN5-6 refers to a publication showing no TSNAs were detected, additional publications have also reported on the presence of TSNAs in e-liquids (3,6). TPD requires the use of high purity ingredients with various national standards (8,9) clarifying this means the use of pharmaceutical grade purity.

See Table 1, answer 7.

P30, LN32: states more than 7000 flavours were reported in 2014 (10), where the researchers classified a flavour as one having a unique linguistic label, as opposed to being based on flavour ingredients. A more recent survey of the Dutch market by Havermans et al. (11), classified 16,300 e-liquids into 245 unique flavour descriptions.

See the reply to comment 131.

P30, LN26: states tobacco alkaloids as impurities of nicotine, the publication by Flora et al. (3) reports nicotine-related impurities were either below limits of quantification or were quantified were less than 3% of the nicotine concentration and within ICH guideline Q3B (R2), 2006 (12).

See also reply to comment 193

P30, LN31: refers to Table 6 as showing common flavours, whereas Table 6 (P38) shows data relating to exhaled aerosol.

See above, reply to comment 113.

P30, LN34-38 & P36, LN12-20: refer to presence of diacetyl as a flavouring based on the publications of Klager et al. (13) and Farsalinos (14), using products sourced from the US or pre-TPD from EU countries. Furthermore, diacetyl is not listed an ingredient in Appendix 2 of the report.

Diacetyl has been listed an ingredient in Appendix 2 of the report.

P31, LN6-7: refers to the formation of aldehydes at temperatures of 350 and 600 degrees C, no context is given to the range of temperatures typical of e-cigarettes.



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115	Compernelle Thomas, British American Tobacco, Belgium	6.5.2 Exposure assessment	<p>We respectfully request SCHEER to correct and amend the following:</p> <p>P32,Table 3: data from Visser et al. (1,2) covering up to 17 products, are representative of those available at the time and therefore may not reflect more modern designs of products.</p> <p>P33,LN14: nicotine transfer to e-aerosol is impacted by PG/VG composition and device power Kosmider et al. (3).</p> <p>P33,LN26-27: data for glycerol and glycols in aerosol have been published (1).</p> <p>P35,Table 4 lists data from Goniewicz et al., 2014, however there are two entries for Goniewicz et al., published in 2014, within the references section of the report.</p> <p>P35,LN13-15: clarification should be added to state that 9 of the 11 VOCs tested for were not found in the aerosol of the 12 products tested. Data on selected VOCs have be published (4,5).</p> <p>P36,LN5-8: TSNA data in Goniewicz et al. (7) have not been replicated and relate to products that are no longer commercially available, additional publication listed in section 6.5.2 (4-6).</p> <p>Visser et al. (1) report summarizes “A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.” Thus the substances of primary interest regarding e-cigarette exposure are formaldehyde, acetaldehyde, acrolein and trace metals in the aerosol.</p> <p>P37,LN9-10: use of maximum values of compounds as reported by Visser et al., (1,2) does not represent concentrations that would be measured from more modern designs of e-cigarettes.</p> <p>P38,LN15-22: second-hand exposure risk assessment uses maximum values reported by Visser et al. (8), based on popular products tested in the research by Visser et al. (2) and is therefore</p>	<p>See Table 1, Answer 8.</p> <p>See Table 1, Answer 4.</p> <p>No changes needed.</p> <p>No changes needed.</p> <p>See Table 1, Answer 4.</p> <p>See Table 1, Answer 4.</p> <p>See Table 1, Answer 4.</p> <p>See the reply to coment 96.</p> <p>See the reply to coment 96.</p>
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of limited relevance to current products. The data are based on 17 volunteers with considerable variation in average exhaled volume ranging from 33 to 1528 mL, noted as not representative for normal exhalation or breathing volumes (9).

See Table 1, answer 4.

Exposure estimates for the evaluation of local effects on respiratory tract assumes a retention factor of zero, thus implying that the volunteer does not retention any of the inhaled aerosol and its constituents. In addition, measurements were based on single exhalations. Other researchers have employed measurements of the aerosol in air (10-13). One of the scenarios used for the exposure estimates assumed 480 puffs over a 4 hr period, would not be considered realistic based on the values quoted in section 6.5.5.3 of the report, P57, LN5-10.

See Table 1, answer 8.

P39, LN12: refers to the presence of formaldehyde and acetaldehyde in exhaled air, but no supporting evidence is provided within the report, table 6 reports these as <LOQ along with acrolein.

See the reply to coment 96.

We would kindly refer SCHEER to the literature attached providing more recent and appropriate methodology for the assessment of aerosol constituents in e-cigarettes.



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116 Olteanu Vlad, Juul Labs Inc., Belgium

6.5.2 Exposure assessment

This analysis of risk exposure studes ignored swathes of published literature and generally lacks robustness.

With regard to the selection of literature: see Table 1, answer 2.

For example, this report comes to a conclusion on the characteristics of e-cigarette aerosol based on a handful of studies, ignoring numerous papers that have been published (McAuley et al., 2012; Bertholon et al., 2013; Zhang et al., 2013; Fuoco et al., 2014; Marini et al., 2014; Mikheev et al., 2016; Montigaud et al., 2021).

Mikheev et al (2016) was cited. Montigaud et al, clearly was published after publication of the preliminary Opinion. Montigaud et al. is a model study on regional deposition of e-cig emissions and this has no direct relevance for the risk assessment.

The discussion of aerosol characteristics including particle number concentration and size distribution shows a lack of understanding

Ingebretsen et al (2012). has been included in the opinion

as to the dynamic nature of e-cigarette aerosols. The constantly changing nature of the aerosol means that instruments are limited in measurement of particle size distribution and geometric standard deviation. This has been discussed in detail by Ingebrethsen et al (2012).

Conclusions on second-hand exposure (Page 38, line 14 Page 39, 24) were reached on the basis of 3 studies, one of which does not cover pod-based systems (Visser et al 2019), which are constantly referenced throughout the opinion. And the assertion on Page 39, Line 18 that there is a scarcity of data on second-hand exposure is simply not correct.

Studies omitted from consideration here include several that measured air concentrations of selected constituents where e-cigarettes are or have been used (Balbe et al., 2014; Zwack et al. 2017; Khachatoorian et al. 2019; Nguyen et al. 2019) and some that also measure biomarkers of exposure (Chorti et al. 2012; Kouretas et al. 2012; Flouris et al. 2012, 2013; Johnson et al. 2019).

Several studies that examine constituents in exhaled breath were also omitted, including Long 2014; Marco and Grimalt 2015; St. Helen et al. 2016; Samburova et al. 2018; and Papaefstathiou et al. 2020.

The conversion factors between Table 5 and other Tables presented in the Opinion are confusing, and there is no rationale presented for why the data is presented in this manner. The values presented are extrapolated from concentrations in each puff (mass per puff/70 mL puff volume), defined as mass per 70mL puff volume to mass per L. This puff volume is not feasible in real-world scenarios, but it is not enough information is given to determine if this is a typo or if this is the intended calculation.

The conclusion of the three studies considered for the SCHEER opinion was that, for by-standers, “reported concentrations are orders of magnitude lower for all these substances than those reported for exposure of electronic cigarette users” (Page 39, lines 13-14). But the report disregards this conclusion on the basis that

The Visser studies are the only experimental studies available with controlled conditions and realistic use topography, whereas the risks are estimated using the MoE approach. The literature suggestions have been evaluated and added where appropriate and within the literature selection criteria (see Table 1, answer 2), The SCHEER risk assessment did not consider vape shop air or surfaces.

See Table 1, answer 4.

No changes needed.

The conversions are based on the puff volumes reported in the various studies and not on a fixed puff volume of 70 mL.

This is the intended calculation for an unitary view about the chemical components present in these tables.

The exposure assessment results are considered in the conclusions on second-hand exposure risks in Section 6.5.5.6., taking together the different lines of evidence (exposure/hazard/MoE calculations). One of the lines of evidence is “

the weight of evidence (Woe) is weak. However, the inclusion and objective evaluation of the substantial number of studies on second-hand exposure in the literature would likely lead to a different conclusion on Woe.

These studies also provide a robust data set that provides a high degree of confidence in the conclusions. We believe that objective evaluation of all of these studies, especially those that contain contemporaneous comparison to combustible cigarettes provides a consistent conclusion that except for propylene glycol and glycerin, the potential constituent exposure to exhaled constituents and particulate matter are orders of magnitude less than from combustible cigarettes. A number of quoted studies were uploaded with this submission as either a full .pdf or as a first page .jpg as allowed by the 1MB file limit or copyright rules. Please fully respect copyright rules as described in the upload studies.

Ref:

Samburova et al. (2018). Aldehydes in Exhaled Breath during E-Cigarette Vaping: Pilot Study Results. *Toxics* . 2018 Aug 7;6(3):46. doi: 10.3390/toxics6030046.
 Papaefstathiou et al (2020). Breath analysis of smokers, non-smokers, and e-cigarette users. <https://doi.org/10.1016/j.jchromb.2020.122349>
 Flouris et al (2012). Acute effects of electronic and tobacco cigarette smoking on complete blood count. <https://ir.lib.uth.gr/xmlui/handle/11615/27500>
 Ingebrethsen et al (2012). Electronic cigarette aerosol particle size distribution measurements. DOI: 10.3109/08958378.2012.744781
 Khachatoorian et al(2019). Identification and Quantification of Electronic Cigarette Exhaled Aerosol Residue Chemicals in Field Sites. doi:10.1016/j.envres.2018.12.027.
 Johnson (2019). A biomonitoring assessment of secondhand exposures to electronic cigarette emissions. doi:10.1016/j.ijheh.2019.04.013

Exposure of bystanders to glycerol or aldehydes is negligible or orders of magnitude lower than for electronic cigarette users”. Literature suggestions from the public consultation have been evaluated and prompted the SCHEER to adapt the conclusion on the Woe for second-hand exposure to “moderate”. The conclusions have been adapted accordingly.

See Table 1, answer 4

117	Olteanu Vlad, Juul Labs Inc., Belgium	6.5.2 Exposure assessment	<p>This analysis of risk exposure studies ignored swathes of published literature and generally lacks robustness.</p> <p>For example, this report comes to a conclusion on the characteristics of e-cigarette aerosol based on a handful of studies, ignoring numerous papers that have been published (McAuley et al., 2012; Bertholon et al., 2013; Zhang et al., 2013; Fuoco et al., 2014; Marini et al., 2014; Mikheev et al., 2016; Montigaud et al., 2021).</p> <p>The discussion of aerosol characteristics including particle number concentration and size distribution shows a lack of understanding as to the</p>	See reply to comment 116.
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dynamic nature of e-cigarette aerosols. The constantly changing nature of the aerosol means that instruments are limited in measurement of particle size distribution and geometric standard deviation. This has been discussed in detail by Ingebrethsen et al (2012).

Conclusions on second-hand exposure (Page 38, line 14 Page 39, 24) were reached on the basis of 3 studies, one of which does not cover pod-based systems (Visser et al 2019), which are constantly referenced throughout the opinion. And the assertion on Page 39, Line 18 that there is a scarcity of data on second-hand exposure is simply not correct.

Studies omitted from consideration here include several that measured air concentrations of selected constituents where e-cigarettes are or have been used (Balbe et al., 2014; Zwack et al. 2017; Khachatoorian et al. 2019; Nguyen et al. 2019) and some that also measure biomarkers of exposure (Chorti et al. 2012; Kouretas et al. 2012; Flouris et al. 2012, 2013; Johnson et al. 2019).

Several studies that examine constituents in exhaled breath were also omitted, including Long 2014; Marco and Grimalt 2015; St. Helen et al. 2016; Samburova et al. 2018; and Papaefstathiou et al. 2020.

The conversion factors between Table 5 and other Tables presented in the Opinion are confusing, and there is no rationale presented for why the data is presented in this manner. The values presented are extrapolated from concentrations in each puff (mass per puff/70 mL puff volume), defined as mass per 70mL puff volume to mass per L. This puff volume is not feasible in real-world scenarios, but it is not enough information is given to determine if this is a typo or if this is the intended calculation.

The conclusion of the three studies considered for the SCHEER opinion was that, for by-standers, “reported concentrations are orders of magnitude lower for all these substances than those reported for exposure of electronic cigarette users” (Page 39, lines 13-14). But the report disregards this conclusion on the basis that the weight of evidence (WOE) is weak.

However, the inclusion and objective evaluation of the substantial number of studies on second-hand exposure in the literature would likely lead to a different conclusion on WOE.

These studies also provide a robust data set that provides a high degree of confidence in the conclusions. We believe that objective evaluation of all of these studies, especially those that contain contemporaneous

			<p>comparison to combustible cigarettes provides a consistent conclusion that except for propylene glycol and 1,3-glycerine, the potential constituent exposure to exhaled constituents and particulate matter are orders of magnitude less than from combustible cigarettes.</p> <p>A number of quoted studies were uploaded with this submission as either a full .pdf or as a first page .jpg as allowed by the 1MB file limit or copyright rules. Please fully respect copyright rules as described in the upload studies.</p>	
118	Vuerich Michela, A NEC, European Consumer voice in standardisation, Belgium	6.5.2 Exposure assessment	<p>6.5.2.1 Aerosol characteristics Page 29, lines 1-2: The CORESTA recommendations (3.0 sec puff duration and 55 mL puff volume) are representative for 1st and 2nd e-cigarettes and, therefore, probably outdated. Puff volumes of 100 – 150 ml seem more appropriate.</p> <p>6.5.2.2 Exposure to aerosols, qualitative description Page 30, lines 33-35: The Klager et al. (2017) study found “that diacetyl and acetoin were the most prevalent of the flavouring chemicals in electronic cigarette aerosols being found in more than 60% of samples”. It is then astonishing that these substances are not included in Table 2 (most frequently used ingredients in e-liquids other than nicotine).</p> <p>Page 30, lines 36-35: Diacetyl and/or acetylpropionyl were found in over 70% of sampled liquids and their aerosols (Farsalinos et al., 2015a). It is then astonishing that these substances are not included in Table 2 (most frequently used ingredients in e-liquids other than nicotine).</p> <p>6.5.2.3 Quantification of aerosol concentrations Page 37, lines 9-10: It is difficult to understand why only the Visser et al. studies (2014 and 2015) have been chosen for the risk assessment rather than the full range of available studies.</p>	<p>See answer to the comment 113.</p> <p>The references list has been updated.</p>
119	Woessner Julie, International Network of Nicotine Consumer Organisations	6.5.2 Exposure assessment	<p>Pages 28-30</p> <p>The use of the terms “droplets” and “particles” is somewhat misleading. SCHEER should define these terms and explain the difference between the two to prevent confusion. A comparison with tobacco smoke would also be helpful here to help clarify the difference.</p>	<p>Section 6.5.2.2 gives an impression of the compounds that can be encountered in aerosol inhaled by users of e-cigarettes and 6.5.2.3 an overview of quantitative levels reported. However, in the next step SCHEERs prioritizes, selecting relevant compounds for the RA in electronic cigarette aerosols in the EU. See p.19</p>

	ons (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU		<p>Page 30 / Lines 36-38 Note that Farsalinos study 2015 was performed several years ago, and industry has since instituted controls to avoid the problems highlighted by this study.</p> <p>Page 31 / Line 32 Using the term “smoulder” is misleading, as it relates to the combustion process and not to vaping. The more appropriate reference would be “electronic cigarettes do not produce aerosol when no puff is being taken.</p> <p>Page 32 / Line 4 Using “smoking device” is misleading. It fails to respect SCHEER’s own terminology as defined on page 19.</p> <p>Page 27, line 56; Page 32, line 2; Page 32, line 7; page 33, line 31; pages 33-35/Table 4; page 36, line 13; page 36, line 17; page 36 line 23: Using “test machine” would be better as vaping devices don’t emit smoke.</p> <p>Page 36 / line 34 Using “electronic cigarette smoking” is misleading and inaccurate. It doesn’t respect SCHEERs own terminology as defined on page 19.</p>	<p>SCHEER has added a sentence to this section warning for the fact that some exposure data may not apply any more or may only be valid in specific countries.</p> <p>The SCHEER agrees. It has been corrected.</p> <p>Rephrased the literature papers have been published both terms.</p> <p>The SCHEER agrees. It has been corrected.</p> <p>Rephrased the literature papers have been published both terms.</p>
120	Moiroud Jean, Fédér ation Interprofes sionnelle de la Vape (FIVAPE), France	6.5.2 Exposure assessment	<p>P. 30, lines 24-25: ethylene glycol is not present in European e-liquids. This US source seems irrelevant in this context.</p> <p>P. 31, lines 23: The sources used in this report shouldn’t be partially used (Visser et al.). A small proportion of liquids might contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the vast majority of e-liquids sold within the EU.</p> <p>P. 31, lines 29-53: ‘Second-hand exposure’: Some publications show a very strong retention of aerosol constituents. This would make passive exposure to the aerosol of an electronic cigarette</p>	<p>Section 6.5.2.2 gives an impression of the compounds that can be encountered in aerosol inhaled by users of e-cigarettes and 6.5.2.3 an overview of quantitative levels reported. However, in the next step SCHEERs prioritizes, selecting relevant compounds for the RA in electronic cigarette aerosols in the EU. See also Table 1, Answer 42.</p> <p><i>SCHEER added a sentence to this section warning for the fact that some exposure data may not apply any more or may only be valid in specific countries.</i></p> <p>The SCHEER believes the data shown are confirming this comment. The SCHEER took into consideration all the literature sources, in order to elaborate a complete opinion.</p>

negligible.

So://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/

P. 32, table 3 on nitrosamines: a small proportion of e-liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids (Visser et al.).

Viser et al., has been completed with other literature sources, as mentioned above.

P. 33, lines 19-23: The conditional is missing. The amount of nicotine emitted by an electronic cigarette is highly variable and can be compared to that of a tobacco cigarette under certain specific conditions only. In others, it is much lower. So://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837998/

The text has been reprased and the suggested source was added.

P. 36, lines 4-7: TSNAs shouldn't be part of the risk assessment for e-cigarette but only for those with tobacco extracts or heated tobacco. Only a small proportion of e-liquids contain diethylene glycol, benzene, toluene or TSNAs. Those substances were not demonstrably present in the great majority of liquids (Visser et al.).

The SCHEER included only measurable constituents. Viser was completed with other sources.

See Table 1, Answer 4.

P. 37, lines 6-7: nitrosamines if tobacco extract is added to the e-liquid.

The literature source was added.

P. 37, lines 9-10: the risk assessment shouldn't be made with nitrosamines. In Visser et al 2014, it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."

See table 1, answer 4.

P. 38, lines 4-6: For carbonyl emissions in order to avoid risk of dry puff condition, the generation process should a vaping machine (not a smoking machine) as defined in the ISO 20768. Smoking machine are used with device at the horizontal devices, when vaping machine allows puffing generation with a 45° (as e-cigarettes are used) angle reducing risks of dry puff (i.e. AFNOR XP D90-300-3 standard).

Risk of dry-hits can indeed be reduced when devices are held under an angle. In the report of Visser et al 2014, e-cigarettes were always completely filled, and a human assessor checked whether dry-hits occurred.

Agree with this clarification.

AFNOR XP D90-300-3 standard and related standards have been added to this opinion.

P. 38, table 6 on nitrosamines: nitrosamines can only come from e-liquids containing tobacco extracts. In Visser et Al (2014), it is said

Viseer et al 2014 has been completed with other literature sources.

that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."

Ref:

St Helen et al. (2016). Nicotine delivery, retention, and pharmacokinetics from various electronic cigare://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/

Talih et al. (2015). Effects of User Puff Topography, Device Voltage, and Liquid Nicotine Concentration on Electronic Cigarette Nicotine Yield: Measurements and Model Predict://www.ncbi.nlm.nih.gov/pmc/articles/PMC4837998/

121 No agreement to disclose personal data

6.5.2 Exposure assessment

p.30, 12: The Opinion extensively discusses the number and size of particles emitted by electronic cigarettes without, mentioning that these are liquid droplets, such as aerosol particles emitted by inhalers prescribed to patients with asthma or other restrictive lung diseases. Unlike solid particles in tobacco smoke, which cause long-term inflammatory processes in the lung, liquid droplets dissolve when coming into contact with tissues.

See a previous very similar comment (112)

SCHEER lists each substance detected, regardless of its concentration or impact on human health. Also, the Committee's reference to Klager et al., which reported 60% of the liquids tested contained diacetyl or acetoin, was conducted in the United States and, as previously pointed out, is not relevant when taking European Union into consideration, as the use of such substances is prohibited by current legislation.

Section 6.5.2.2 indeed gives an impression of the compounds that can be encountered in aerosol inhaled by users of e-cigarettes and 6.5.2.3 an overview of quantitative levels reported. However, in the next step SCHEERs prioritizes, selecting relevant compounds for the RA in electronic cigarette aerosols in the EU: the solvent carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs), by-products of thermal decomposition of some of these constituents, notably carbonyls, and metals originating from the device. The risk assessment for this selection was subsequently based the aerosol concentrations found in the controlled studies of Visser et al.

Other potentially harmful substances listed in this section are reactive oxygen species, tobacco specific nitrosamines and metals. The concentration of free radicals in e-cigarette aerosols is about 10 times lower than in tobacco smoke (Bitzer et al, 2020) (doc. 13). Tobacco-specific nitrosamines are difficult to detect (Goniewicz et al, 2014) (doc. 14) and metal concentrations are well below internationally accepted thresholds (Farsalinos et al, 2018) (doc. 15).

See Table 1, answer 1.

P.30, 116: In the opinion, SCHEER often compares electronic cigarettes with traditional cigarettes; ANAFE believes that the evaluation of the e-liquids ingredients and emissions should also be related to those of traditional cigarettes. Without such comparison, we would have a partial and non-concrete assessment of the health

The fifth generation has been added, p.21.

			effects of electronic cigarettes and e-liquids.																					
			P.32, 17: The mentioned studies were carried out several years ago with both first and second generation electronic cigarettes: such products are not representative of hardware sold today (defined as fifth generation).	The literature sources refer in majority to the first and second generation electronic cigarettes.																				
			P.36, 122: Regarding metals' concentration, ANAFE would like to mention the study carried out by the University of West Virginia in 2016, which shows that the use of electronic cigarettes does not affect the level of toxic metals in blood and urine. As a matter of fact, the levels detected are equal to those of a non-smoker (doc. 16).	This study by Wiener and Bandhari was not selected, since any exposure to metals in aerosols will hardly be detectable in blood and urine in view of significant background exposures. Therefore it is not surprising that current or former e-cigarette use failed to reach a statistical significance in the association with metals.																				
			P.37, 19: The mentioned studies were carried out several years ago with both first and second generation electronic cigarettes: such products are not representative of hardware sold today (defined as fifth generation).	Unfortunately, this comment does not explain why these studies are not valid and does not offer alternative studies with "fifth generation" devices.																				
122	Emily Saunders, Broughton Nicotine Services, United Kingdom	6.5.2 Exposure assessment	Page 28, starting line 29 – Discusses the need for standardised protocols for puffing. Please note that this is already in place (ISO20768:2018).	Please see the reply to comment 72.																				
123	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.2 Exposure assessment	Page 38, lines 9-12 Please consider that this statement on emissions doesn't put the risk in context against combustibles, or even against standard consumer products (scented candles etc). Carbonyls for example are listed as carcinogenic/cytotoxic (which they are), and the risk has been classed as moderate to low, but these are emitted by many other products, so the question is whether they have significant health effects at the concentrations present in ENDS.	The mandate does not require to compare risks.																				
124	Ciprian Boboi, Asociația Industriei de Vaping (Vaping Industry)	6.5.2 Exposure assessment	<table border="0"> <tr> <td>P</td> <td></td> <td>28</td> <td>-</td> <td>29</td> </tr> <tr> <td>P</td> <td>32/</td> <td>L</td> <td>1</td> <td>-</td> </tr> <tr> <td>P</td> <td>37/</td> <td>L</td> <td>4</td> <td>-</td> </tr> <tr> <td>P</td> <td></td> <td></td> <td></td> <td>40</td> </tr> </table>	P		28	-	29	P	32/	L	1	-	P	37/	L	4	-	P				40	See reply to comment 112.
P		28	-	29																				
P	32/	L	1	-																				
P	37/	L	4	-																				
P				40																				

Association)
,Romania



Exposure_assessment
.pdf

125	Robson Deborah, King's College London, United Kingdom	6.5.2 Exposure assessment	Given that the Committee are tasked with supporting the Commission in assessing the potential need for legislative amendments to the TPD, it is unclear why studies carried out pre-TPD are included in this section (and other sections), as presumably exposures have changed post TPD. Also, why such a heavy reliance on studies conducted in the US, where products, nicotine content, additives, different regulations will influence exposure levels and may be of limited relevance to European vapers.	With regard to literature selection: See Table 1, Answer 2. Of course, post-TPD exposure assessments are preferred, See also Table 1, Answer 8 for use of non-EU data.
126	Ciprian Boboi, Asociația Industriei de Văpărit (Vaping Industry Association), Romania	6.5.2 Exposure assessment	<p>Line # P 28 - 29</p> <p>SCHEER extensively discusses the number and size of particles emitted by e-cigarettes without mentioning that they are liquid droplets, like the particles in fog or the aerosol emitted by metered-dose inhalers prescribed to patients with asthma or other restrictive lung diseases. In contrast to the solid particles in tobacco smoke, which cause long-term inflammatory processes in the lung, liquid droplets dissolve upon contact with tissue. Their size determines the site of deposition (oral cavity, upper airways, or lung) but is otherwise irrelevant.</p> <p>SCHEER lists every substance that has ever been detected in e-liquids or aerosols, regardless of their concentrations or their impact on human health. The committee's reference to Klager et al., who reported that 60 % of tested liquids contained diacetyl or acetoin, was conducted in the United States and is not relevant to the European Union where the use of such substances is prohibited by current legislation.</p> <p>Other potentially harmful compounds listed in this section are reactive oxygen species, tobacco-specific nitrosamines, and metals. The concentration of free radicals in e-cigarette aerosols is about 10-fold lower than in tobacco smoke (Bitzer et al, (2020)) (https://pubs.acs.org/doi/10.1021/acs.chemrestox.0c00088).</p> <p>Tobacco-specific nitrosamines are hardly detectable (Goniewicz et al (2014)) (https://pubmed.ncbi.nlm.nih.gov/23467656/), and the concentrations of metals are far below internationally accepted thresholds (Farsalinos et al (2018))</p>	See reply to previous comment on particles (112).

(<https://pubmed.ncbi.nlm.nih.gov/30384783/>)

P 32; L 1 - 20
P 37; L 4 - 12

The data in table 3 shows only the levels of the identified substances in e-cigarette aerosol. However, this data lacks context or meaning when not read in conjunction with the requisite data for combustible cigarettes.

RIVM has collected significant data on these points, and, surprisingly, this is not considered relevant. This flaw in the Committee's approach - comparing the risks of e-cigarettes with the risk of no use rather than with the use of cigarettes - is evident in its conclusions on p37. These conclusions completely fail to identify the relative risk with cigarette smoking as a critical factor when considering its risk assessment protocol.

P 40;

It is stated that 60 mg of nicotine is fatal for humans. The 60-mg estimate, which would implicate nicotine toxicity comparable to that of the deadly poison cyanide, was based on erroneous self-experiments performed in the mid of the 19th century and has been corrected to 0.5 - 1 g several years ago, as per Mayer (2014) (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/>).

See replies to comment 112 and 193.

127 Juusela Maria, Doctors against tobacco (DAT) Finland, Finland

6.5.2 Exposure assessment

Safety of chemicals has to be studied before use, and if harmful effects are identified, but the use is regarded as essential, warnings and advice about safe use needs to be included in packages and product information. In chemical risk assessment it is not feasible to wait until there is conclusive epidemiological information. Rather than counting sick and dead, the safety is studied in laboratory animals and in in vitro test systems, on basis of which it is possible also to consider mechanisms of action. On basis on such studies and exposure information risk assessment of potential health effects is carried out. As to nicotine, it has been known for a long time that it is very toxic. (Baumung et al.2016)

Thank you. The SCHEER believes to have followed such approach.

Ref:

Baumung et al (2016). Comparative risk assessment of tobacco smoke constituents using the margin of exposure approach: the neglected contribution of nicotine. Scientific Reports 6:35577 DOI: 10.1038/srep35577

128 Mayer Bernhard-

6.5.3 Hazard identification of

page 40, lines 5-11
If 60 mg of nicotine were fatal for humans, nicotine toxicity would

Michael,Pharmacology & Toxicology, University of Graz,Austria

most relevant compounds

be comparable to that of the deadly poison cyanide. However, in contrast to cyanide, nicotine has been used very rarely for homicides and suicides, and most suicide attempts with nicotine failed. The 60-mg estimate is based on erroneous self-experiments performed in the mid of the 19th century and was corrected to 0.5 - 1 g several years ago [1].

See replies to comment 112 and 193.

The inhibitory action of nicotine, conferring neurotoxicity, occurs at very high plasma concentrations, which arise only upon applying large amounts of nicotine as a bolus, e.g., by intravenous injection. Upon inhalation of small amounts of nicotine by smoking or vaping, metabolism, distribution, and elimination limit plasma concentrations to a steady-state of about 30 ng/ml [2], which is around 100-fold below the threshold of lethality [1].

Because of the low toxicity of nicotine, consumers won't even notice unintentional spilling over the skin or swallowing small amounts of e-liquid. The number of calls at poisoning centers reflects the public's unsettlement due to scaremongering by public health rather than severe cases.

The current TPD2 limit of the nicotine concentration in e-liquids (20 mg/ml) results from horse-trading in the trilogue meeting and not justified by toxicology. Similarly, the limit of container size to 10 ml causes plastic waste production without protecting public health. European consumers purchase sets consisting of 20 x 10-ml instead of one 200-ml bottle. Therefore, the 10-ml limit is not incredibly helpful in the EU's fight against plastic waste.

page 41, lines 51-57

There is no evidence that menthol increases users' exposure to nicotine through increasing "the absorption and lung permeability of aerosol". Even if it did, this would have no adverse health outcome, because smokers and vapers unconsciously adjust their plasma nicotine concentrations to the desired levels (see, [3] and references therein). Menthol may mask the airway irritation by tobacco smoke, but the opposite is true for nicotine-containing aerosols from e-cigarettes. Menthol enhances (!) the perceived airway irritation and harshness produced by inhalation of e-liquid

The reference to the SCENIHR Opinion was referring to the hazard identification of important flavourings. For risk assessment of electronic cigarettes, the concentration in the aerosol from the e-liquids have been considered. The Opinion has been changed accordingly

containing less than 24 mg/ml of nicotine [4]. Rosbrook et al. confirm e-cigarette users' experience who prefer menthol-containing e-liquids to increase the desired airway sensation (throat hit) caused by the inhalation of propylene glycol in combination with nicotine. Therefore, menthol will certainly not "increase the likelihood of nicotine addiction in adolescents and young adults," as stated by the SCHEER.

1. Mayer. Arch. Toxicol. 88, 5-7 (2014)
2. Hukkanen et al. Pharmacol. Rev. 57, 79-115 (2005)
3. Dawkins et al. Psychopharmacology (Berl) 233, 2933-2941 (2016)
4. Rosbrook et al. Nicotine Tob. Res. 18, 1588-1595 (2016)

129	No agreement to disclose personal data	6.5.3 Hazard identification of most relevant compounds	In the assessment of nicotine concentration in the aerosol of e-cig, the opinion does not take into account the results of the study by Pacifici R et al. 2015, which showed that the switch to electronic smoking does not generate an increase in the nicotine consumption in non-dual electronic smokers. Such an evidence is important and should be considered particularly in high cardiovascular risk smokers: the absence of combustion (and the consequent significant lower exposure to its toxicants) is a net and high advantage as the combustion products are mostly responsible for the cardiovascular harm and not the nicotine.	Please see Table 1, answer 1.
130	Carbonara Giovanni, Anpvu,Italy	6.5.3 Hazard identification of most relevant compounds	Nicotine is a toxic compound that should be handled with care, but the frequent warnings of potential fatalities caused by ingestion of small amounts of tobacco products or diluted nicotine-containing solutions are unjustified and need to be revised in light of overwhelming data indicating that more than 0.5 g of oral nicotine is required to kill an adult.” “There is a mismatch between the generally accepted lethal oral nicotine dose of 60 mg, resulting in approximately 180 µg L-1 plasma concentration, and the 4.4- to 8.9-fold higher lethal plasma concentrations we found in cases of e-liquid intoxication.”	In 2014, Professor Bernd Mayer of the Department of Pharmacology at Karl-Franzens University Graz published a report detailing actual amount of nicotine absorbed by the human body. Mayer claims "smoking a cigarette results in uptake of approximately 2mg of nicotine and gives rise to mean arterial plasma concentrations of about 0.03mg/L." See replies to comment 112 and 193.
131	Martinez Javier, JT International SA, Switzerland	6.5.3 Hazard identification of most relevant compounds	P.41, 1.34-36 Please revise the wording, “Besides possible toxic effects after inhalation, these chemicals may confer a characterising flavour to the e-liquid meaning a clearly noticeable smell or taste as for maltol, menthol or vanillin, thus contributing to attractiveness of electronic cigarettes.” Please consider that addition of flavour compounds to e-liquids allows for product differentiation, similar to addition of flavour compounds to other consumer products.	See Table 1 answer 7. Furthermore, the section mentioned has been removed from the final Opinion, to prevent overlap with section 6.6.

SCHEER refers to 'attractiveness'. Nonetheless, SCHEER fails to: 1) provide a definition of the term, 2) provide a method to assess 'attractiveness', and 3) to consider that preference(s) for flavours and products is highly subjective. Please refer to Shiffman 2015 that examined non-smoking teens' interest in using e-cigarettes and found that flavour descriptors had no significant impact. Interest in e-cigarettes was very low and did not vary significantly by the different flavour descriptors. The authors concluded, "These data do not support the hypothesis that adding flavours to e-cigarettes will attract interest among non-smoking teens who had not used e-cigarettes, as flavour descriptors had no significant influence on non-smoking teens' interest in using e-cigarettes."

P.41, 1.38-41 We note that the sentence, "Indeed, the flavours by providing a specific and standardised taste, makes an e-liquid unique and recognisable among the large variety of available brands, thus binding the consumer (Havermans et al., 2019)" is not supported by the reference provided. The current sentence in the SCHEER report implies that flavour chemicals alone set an e-liquid apart from other products and force continued use by the consumer. However, the paper by Havermans et al. merely concludes, "The variety of marketed flavour descriptions reflects flavour preference of e-cigarette users as described in literature".

P.41, 1.45-49 We note that SCHEER does not provide any scientific study to support their claims: "Indeed, it can be achieved, for example, by adding chemicals increasing the bioavailability of nicotine, altering the pH of the liquid or facilitating the inhalation, as in the case of additives with local anaesthetic effects such as menthol." Please provide compelling scientific references to support these statements or remove the statements.

P.41, 1.51-57 We note the speculative nature of SCHEER's statements absent of appropriate supportive study provided: "It may increase the absorption and lung permeability of aerosol, thereby increasing nicotine uptake while decreasing the irritation from nicotine. This action may increase the likelihood of nicotine addiction in adolescents and young adults who experiment e-

This section has also been removed, to prevent overlap with section 6.6.

Regarding these effects of menthol, the SCHEER uses careful wording. The effect of menthol has been well-studied in cigarette smoking. The nicotine dose may not be affected due to consumers adapting their behaviour. In Krishnan-Sarin 2017, users used their e-cigarette according to a prescribed protocol. In

			cigarettes and make it more difficult to quit. (SCENIHR 2016).” The SCENIHR 2016 reference pertains to menthol’s role in combustible cigarettes; it does not provide any data or refer to any studies or research assessing the role of menthol in e-cigarettes as a reinforcer of use behavior. We draw SCHEER’s attention to an independent scientific study that examined whether flavors inhaled through an e-cigarette would enhance the acute rewarding effects of nicotine administered intravenously. (MacLean et al., 2020). The results indicate that neither the cognitive nor the physiological effects of nicotine were affected by any flavor condition. The authors commented, “The present findings did not support an interaction between IV-nicotine dose and inhaled flavor for acute effects of nicotine.” concluding, “flavor had minimal to no effect on the acute effects of nicotine.” See also Krishnan-Sarin et al. 2017, indicating no menthol-related changes in stimulant effects, nicotine withdrawal symptoms or ad-libitum use.	addition, the authors write: we provide human behavioral evidence that inclusion of menthol, even at very low concentrations, can increase the appeal of e-cigarettes among youth.
132	Poirson Philippe, Sovape, France	6.5.3 Hazard identification of most relevant compounds	[p. 40 l. 10] The DL50 of nicotine is around 0,5 g (Mayer 2013) [p. 40 l. 13-17] Not relevant in the TPD context with only pharmaceutical grade nicotine in liquids. [p. 40 l. 19-30] Not relevant about nicotine if not in fermented tobacco. [p. 41 l. 36-38] This is a subjective commentary without scientific reference. [p. 41 l. 45-49] Commentary without clear scientific reference [p. 42 l.14] Dusautoir 2020 must be integrated to this report. [p. 42 l. 16 to p. 45 l. 38] Must be revised with reference to the Farsalinos 2018 study on metal emissions compared to safety standards.	See replies to comment 112 and 193. Small amounts of impurities may be present even in the pharmaceutical grade nicotine. The SCHEER evaluation is related to ingredients of the aerosol from electronic cigarettes Based on these comments the text on page 41 of the preliminary Opinion was revised. This study was added to the Risk Assessment section.
133	Champagnac Maxime, Phode, France	6.5.3 Hazard identification of most relevant compounds	p41 lines 34 to 41 "Besides possible toxic effects after inhalation, these chemicals may confer a characterising flavour to the e-liquid meaning a clearly noticeable smell or taste as for maltol, menthol or vanillin, thus contributing to attractiveness of electronic cigarettes. Flavourings can stimulate electronic cigarette use,	See the reply to comment 131.

especially among vulnerable groups such as non-smoking adolescents, thereby increasing exposure to potentially toxic ingredients. Indeed, the flavours by providing a specific and standardised taste, makes an e-liquid unique and recognisable among the large variety of available brands, thus binding the consumer 40 (Havermans et al., 2019). "

It is a personal statement of the author not supported by a study. it is in the introduction and without any data.

This position "Because the vast range of flavoured e-liquids is attractive to vulnerable consumer groups (eg, adolescents and young adults), there is a clear need for regulation. " in Havermans & al.2019, isn't scientifically argued . (no citation) it is a personal statement of the authors arguing for a need of regulation using a comparison with flavoured cigarette which are proved to be addicted and unhealthy. It is not the aim of the study to prove flavor attractiveness in vaping product.

134 Champagnac Maxime,Phode,France

6.5.3 Hazard identification of most relevant compounds

p48 line 26-28 "The acute sympathomimetic effect of nicotine containing electronic cigarette can possibly be associated with increased cardiac risk populations with and without known cardiac disease. (Moheimani et al., 2017)."

The Moheimani study has been excluded from the Opinion.

This study is not relevant ,with only 43 participants. The control group is biased, (male /female ratio; former smoker ratio 10/16 vs 2/18; period of smoking cessation 2,3years vs 13 years). The cardiovascular effect could be linked to the past cigarettes consumption as there were 10(/16) former smoker in the e-cig group and only 2(/18) in the control group.

135 Champagnac Maxime,Phode,France

6.5.3 Hazard identification of most relevant compounds

p48 lines 30-33 "Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells. Most electronic cigarettes containing nicotine have a basic pH > 9, which seems to enhance the dosage of nicotine delivered (Stepanov and Fujioka, 2015)."

A study from 2015 is not recent for a 10 years product old. This recent study have to be considered to update the Scheer position https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-

The update on the Cochrane review has been included in the Opinion.

			unwanted-effects-when-used What are the results of our review? The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes. // Authors' conclusions: [...]We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.	
136	Becher Rune,Norwegian Institute of Public Health,Norway	6.5.3 Hazard identification of most relevant compounds	Regarding the calculations of health risk for individual components, we miss a presentation of the curves for calculation of Benchmark dose lower bound (BMDL) as a starting point for calculation of margin of exposure (MOE). Although the assessments of nicotine's health effects are well described for cardiovascular disease, this is not the case for other health outcomes, including pregnancy outcomes, where there is reason to believe that results from regular smoking tobacco and snus are highly relevant.	Conclusions are based on the pertinent literature, as explained in the risk assessment section 6.5.5. This literature is predominantly not based on determination of the BMDL, but on the estimation of the Margin of Exposure, comparing Points of Departure, mostly NOAELs from toxicology studies with the results of the exposure assessment. For comparison with smoking: see Table 1, answer 1.
137	Vejdovszky Katharina, AGES – Austrian Agency for Health and Food Safety,Austria	6.5.3 Hazard identification of most relevant compounds	6.5.3 Hazard identification On page 41, lines 18-22, regarding the hazard identification of carriers, a reference is stated that gives details to toxicological features of propylene glycol and glycerol. However, several times ethylene glycol is also mentioned as common carrier of e-liquids (page 30, lines 24-25; page 39, line 35). Why is there no hazard identification given for ethylene glycol?	See Section 6.5.5.1 and Table 5 for an explanation on the prioritisation of chemicals for the risk assessment.
138	No agreement to disclose personal data	6.5.3 Hazard identification of most relevant compounds	Page 39 Line 26: TO MAXIMISE THE PUBLIC HEALTH POTENTIAL OF E-CIGARETTES AND TO ENCOURAGE ADULT SMOKERS TO TRANSITION AWAY FROM TOBACCO CIGARETTES, E-CIGARETTES MUST APPEAL TO CURRENT ADULT SMOKERS This is an intrinsic component of tobacco harm reduction, without which adult smokers will not adopt less harmful alternatives to combustible cigarettes. The Opinion focuses solely on the absolute risk of e-cigarettes, thereby failing to acknowledge and clarify any reduced relative risk potential for adult smokers who would otherwise continue to smoke. The totality of the published scientific evidence shows that whilst e-cigarettes are not risk free, the risks associated with vaping are significantly less than those associated with long term smoking tobacco[1]. This has been extensively	See Table 1, answer 1.

documented and characterised in the UK Government’s Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)’s recent comprehensive report[2]. Moreover, a recent systematic review also concluded that e-cigarette aerosols are substantially less toxic compared to combustible cigarettes or solutions – the most relevant comparison for adult e-cigarette smokers[3].

P42 L18: The Opinion’s review of carbonyl and heavy metals, based on the reported levels in Table 5 (ug/L), and the effects reported in Table 7, fails to acknowledge that many of the adverse effect levels are likely explained by other sources in addition to use of e-cigarettes alone. There are more significant alternative sources for some metals such as the diet and exposure to ambient air/ water which are not explored[4]. We note the values in Table 5, relating to key metals in Table 7, are below workplace exposure levels as set by UK Health and Safety Executive (HSE) and European Environment Agency (EEA). Importantly, this relies on the ability of the regulators to convert the units across the studies to be able to put the different results in to context.



6.5.3_Hazard_identifi
cation_of_most_releva

139	Wyszynska-Szulc, Agnieszka, Philip Morris Products S.A., Switzerland	6.5.3 Hazard identification of most relevant compounds	P. 39	1. 34–45 We suggest removing quantitative references to the levels of harmful and potentially harmful constituents (HPHCs) in e-cigarettes’ aerosols throughout this section, and the document in general, and revise the exposure assessment accordingly, and at minimum include the suggested literature references in the review. The SCHEER’s Opinion suggests an abundance of a range of HPHCs in e-cigarettes’ aerosols, for products on the market today. It is important to note that the cited papers are neither contemporary – i.e. do not reflect the performance of e-cigarettes on the market today, nor are they comprehensive – i.e. they represent a minority of published research results, with the majority of papers showing that the compounds mentioned are generally not detected in commercially available products. For example, impurities such as TSNAs and metals were identified
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in very few samples in several different market surveys and product tests (Farsalinos 2015; Lee 2018; Belushkin 2020). More so, even where trace levels of such impurities were identified in e-liquids, they were generally found to be non-quantifiable in the aerosols or at levels close to the levels found in blank samples (Wagner 2018; Goniewicz 2014; Lee 2018; Beauval 2017). In any case, with the exception of formaldehyde, levels of HPHCs in e-cigarettes' aerosols are systematically reported across commercially available products to be substantially lower than their levels in cigarettes' smoke.

Formation of substances such as VOCs, phenolics, and even carbon monoxide in e-cigarettes' aerosols has indeed been reported (El Hellani 2019; El-Hage2020; Pankow 2017) however such cases are isolated and do not reflect the broader picture of marketed e-cigarettes (Wagner 2018; Nicol 2020; Margham 2016; Rudd 2020; Tayyarah and Long 2014).

More importantly, the SCHEER's Opinion fails to recognize the need for a comparative assessment of the emissions from e-cigarettes to the emissions of the same compounds in cigarette smoke.

P. 42. l. 6-14
In the absence of robust data, we suggest to revise the conclusion that flavourings contribute substantially to aldehyde production in e-cigarettes' aerosols, and at minimum include the suggested literature references below in the review.

It has been reported that the major source of aldehyde production is thermal decomposition of aerosol formers propylene glycol and glycerine (Laino 2011; Laino 2012; Sleiman 2016). Whilst several studies have suggested that flavours may contribute to the formation of selected aldehydes such as acetaldehyde, it is important to note that e-cigarettes are known to exhibit high levels of emissions variability. For example, variability in acetaldehyde levels between different devices was reported in some cases to be as high as 80% of the average across devices (Belushkin 2020). Therefore, whilst the contribution of aerosol formers under dry-puff

In Section 6.5.2.2 it is argued that carbonyls are derived from chemical degradation of components of the e-liquid. Considering the concentrations of carriers as compared to those of flavourings, we can assume, as noted by several authors, that carriers are the main source. The highlighted section does not draw any conclusion on that. The high variability is noted by SCHEER. In the conclusions of the exposure assessment 6.5.2.3.

Thank you for the suggested references. If considered relevant and in line with the selection procedure, the SCHEER included them.

conditions is well characterized, different sources of variability in e-cigarettes' emissions must be assessed before a general conclusion on the role of flavours in aldehyde generation can be made.

P. 41 I. 22 and I. 55-57 and P. 46 I- 2-4
 We suggest deleting the references to the SCENIHR 2016 Opinion on Tobacco Additives I.
 It is mentioned three times that toxicological data on ingredients can be found in the SCENIHR 2016 Final Opinion on Tobacco Additives I. However, as it is correctly pointed out in the instruction of the section, the SCENIHR 2016 Opinion is only valid for ingredients added to cigarettes and roll-your own and, therefore, not applicable to e-cigarettes.



ref-139.docx

The reference to the SCENIHR Opinion was referring to the hazard identification of important flavourings. For risk assessment of electronic cigarettes, the concentration in the aerosol from the e-liquids have been considered .

140 Waław Michalina, Prawo dla ludzi (Law for people),Pol and

6.5.3 Hazard identification of most relevant compounds

In addition, the SCHEER report only says that e-cigarettes "can make smoking more attractive". It does not mention that for many people this offers an alternative to cigarettes. This is somewhat reflected in how the public service perceives vaping. The correct way to steer public health services to truthful information about vaping is to present smokers with a competing 'value'. For many smokers of traditional cigarettes, e-cigarettes are an alternative and help to overcome the addiction. This is confirmed not only by reports published, among others by Public Health England. This is also confirmed in our consultations - every third person, thanks to switching to e-cigarettes, completely gave up taking nicotine in any way.

See Table 1, answer 1.

141 Sweeney Damian ,European Tobacco Harm Reduction Advocates, Ireland

6.5.3 Hazard identification of most relevant compounds

Page 40 lines 10 and 11
 The median lethal dose of nicotine is referred to in the opinion as being 60mg, which equates to 0.8mg/kg for oral ingestion, a figure that is considerably lower than the LD50 of nicotine for mice and rats. This is a highly contested figure and is based on data from over 100 years ago, obtained from questionable experiments. Assuming the figure is correct, which it is not, that would imply nicotine has a similar toxicity as cyanide, which we know is not the case. Mayer (2014) defined the median lethal dose of nicotine to be 20 times

See replies to comments 112 and 193

higher than the 60mg figure that is stated in the opinion. Since one of the main symptoms of nicotine intoxication due to ingestion is vomiting, it can be safely assumed that an even higher volume of nicotine would need to be consumed. The EU already has precautions in place, via the TPD, to prevent against nicotine intoxication, i.e. child-proof caps and a 20mg/ml upper nicotine limit for e-liquids.

Reference uploaded:

Mayer (2014). How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century

142 Bamberger
Claude,Aid
uce,France 6.5.3 Hazard
identification of
most relevant
compounds

6.5.3 Hazard identification of most relevant compounds p40 L10 nicotine "fatal" dose is not 60mg. It has never been (the LD50 evaluated a century ago in a way not conform with OECD standards or basic toxicology and repeated sometimes was). Reference (uploaded) : Mayer, B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol 88, 5–7 (2014). <https://doi.org/10.1007/s00204-013-1127-0>
This error of the 60mg value is also confirmed by (Maessen et al., 2020) "the 4.4- to 8.9-fold higher lethal plasma concentrations we found in cases of e-liquid intoxication".

See replies to comments 112 and 193.

p40 L13 nicotine in vaping products is EP/USP (if I read the TPD transposition from Article 20 §3 d, or if I read AFNOR standards), and the referenced paper (Flora et al. 2017) doesn't imply any risk and measured products before the directive application and in another market.

Risk management is outside the scope of the opinion

An exaggerated fatal dose (confirmed in population by the very low number of cases worldwide, certainly also linked to the presence of child-proof opening for a nearly a decade but not only). A risk not shown from nitrosamines for the users, that can't plausibly exist 2 orders of magnitude lower in persons exposed (one order as inhaled vs exhaled, one order at least as diluted and disappearing in seconds). This makes two "weak to moderate" conclusions weaker and certainly not moderate (abstract p2 L17 and L36).

The WoE part in the Opinion has been revised.

143	Dahlmann Dustin,Independent European Vape Alliance,Germany	6.5.3 Hazard identification of most relevant compounds	P 39; L 34 - 45	The cited paper by Khlystov and Samburova does not represent the current science. Dr Konstantinos Farsalinos, a prominent researcher of e-cigarettes, wrote a letter to the editor of the journal pointing out some of the issues with this manuscript. The paper is not consistent with other similar studies and should not be used as a basis for the SCHEER report. We attach a number of studies that are more representative of the current consensus: Conklin et al (2018) and Farsalinos et al (2018) both found small or zero increases in aldehyde content compared with non-flavoured e-cigarette liquid; these studies should be cited. It should be noted in this context that according to the WHO, ambient air contains between 10 and 200 µg/m ³ of formaldehyde.	The reference has been replaced.
			P 40; L 19 - 30	The report discusses the cancerogenic potential of nicotine based on the presence of N-nitrosamines in trace amounts in tobacco-derived nicotine preparations, including those used in the pharmaceutical industry for the manufacture of nicotine replacement therapies. As e-cigarettes are made using pharmaceutical grade nicotine, these compounds are barely detectable in e-cigarette liquids. Belushkin et al (2020), for example, tested a wide range of e-cigarettes, all of which contained negligible levels of nitrosamines.	Please see Table 1, answer 4. Small amounts of impurities may be present even in the pharmaceutical grade nicotine.
			P 40 - 41; L 33 - 16	Flora et al (2015) provides guidance on how to compare permissible exposure limits to e-vapor product yields. We attach the study “Characterization of potential impurities and degradation products in electronic cigarette formulations and aerosols” and the equation used by the research team. Burstyn (2013) is listed among the citations but does not appear in the text of the report. This study made an early assessment of e-cigarette toxic exposures relative to ‘total limit values’ (TLV) for occupational health exposures. Burstyn concluded: “The vast majority of predicted exposures are <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for	The reference to Flora et al. (2017) has been deleted. The Burstyn study was not included in the final Opinion: see answer to Comment 89.

mixtures was possible.”
 We suggest that a section be added to 6.5.3 that addresses how one might convert exposure limits into a daily exposure amount to facilitate a comparison with permissible exposure limits. Absent this, exposure limits have no context or meaning.

P 41; L 34 - 43
 The Committee has chosen to comment on the use of flavours to make products attractive in this section, despite it being focused on the potential health hazards, indicating that the Committee considers the appeal of e-cigarettes to be a hazard in and of itself. In this respect, the Committee could, in the interests of balance, consider how the existence of an attractive alternative to smoking can be of public health benefit in a Europe where 26% smoke and 700,000 die from smoking related disease annually. In this context, it is worth noting within the report the potential unintended consequences of seeking to make e-cigarettes less attractive. This is discussed at length by the Royal College of Physicians (2016) who conclude: “...if [a risk averse] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking”

This part has been deleted in the final Opinion.



Hazard_identification_of_most_relevant_co

144	Vuerich Michela,A NEC, European consumer voice in standardisation,Belgium	6.5.3 Hazard identification of most relevant compounds	Page 46, lines 8-15: it is difficult to understand why substances which have been identified in a huge number of samples according to the Klager et al. and Farsalinos et al. studies referred to on page 30 have not been included in Table 7 (diacetyl, acetoin, acetylpropionyl) and the preceding text. We believe that also some other substances such as benzaldehyde (cherry flavour) which may be present in high concentrations and which are of concern merit inclusion. We would be also concerned about Cd and Ni not included in the table and the preceding text.	See the explanation of the prioritization procedure in Section 6.5.5.1 and Table 5. Table 7 refers to compounds measured in the aerosol from electronic cigarettes, not in the liquid itself.
145	Schulz Thomas,G	6.5.3 Hazard identification of	P41, Row 18-22, Carriers In this section, the toxicological hazard of propylene glycol should	SCHEER agrees that in relation to PG there are some lines of evidence (human and animal studies) showing irritancy towards the respiratory tract, as submitted

erman Federal Institute for Risk Assessmen t,Germany	most relevant compounds	<p>be elucidated. However, reference was made to the SCENIHR opinion on tobacco additives (2016). In the SCENIHR report, only very few facts are presented and the only reference is the PITOC factsheet from 2012. Therefore, this section is insufficient in its present form. The report should reflect the RAC Opinion on propylene glycol from December 2016 and its background document, which contains many references on studies (in man and in animals). The focus of the paper is on res-piratory irritant effects. Link to the RAC opinion, adopted December, 9th, 2016 https://echa.europa.eu/documents/10162/c02bcec3-641b-6770-a361-99776015680e</p> <p>Link to the Background document. https://echa.europa.eu/documents/10162/1e2a98d4-8ee4-9abc-0167-9f565fed4d0d</p> <p>P41, Row 24, Flavourings Maybe particularly toxic flavourings such as diacetyl should be noted/discussed here. The addition of diacetyl to E-liquids is prohibited in Germany due to its inhalation toxicology. Reference: 17. Bundesgesetzblatt. Zweite Verordnung zur Änderung der Tabakerzeugnis-verordnung, Nr 28 2017 [Available from: http://www.bgbl.de/xaver/bgbl/start.xav?startbk=Bundesanzeiger_BGBL&jumpTo=bgbl117s1201.pd]</p> <p>P41, Row 46-49 and 51-57, menthol There is no doubt that the menthol effect is of great importance when smoking tobacco. In Germany, menthol is completely banned for use in smoking tobacco due to its facilitation of the inhalation of cigarette smoke. Experimental studies at the German Federal Institute for Risk Assessment proved that small amounts of menthol (more than 50 µg menthol per cigarette) are sufficient to trigger a measurable activation of the cold-receptor, namely TRPM8, allowing this effect to take place. (Paschke M, Tkachenko A, Ackermann K, Hutzler C, Henkler F, Luch A (2017) Activation of the cold-receptor TRPM8 by low levels of menthol in tobacco products. Toxicology Letters, 271: 50-57). However, the question is still open, if the menthol effect has the same significance for E-cigarettes as it has for conventional cigarettes.</p>	in the CLH report and assessed by RAC (2016). Though this evidence was not considered to meet the CLP criteria for respiratory irritation STOT SE3; H335, this fact does not discard that a toxicological assessment based on WoE points to possible respiratory irritation effects, under single and repeated exposure.
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146	Olteanu Vlad, Juul Labs Inc., Belgium	6.5.3 Hazard identification of most relevant compounds	<p>Pg 39, Ln 34-45: This section, which cites papers by Khlystov and Samburova, 2016 and Vreeke et al. 2018, states that e-cigarette aerosols contain pyrolysis products including aldehydes that can be toxic and affect different organs. Khlystov and Samburova is not consistent, however, with other similar studies (aldehydes of mg/puff versus mg or ng/puff) and is not appropriate for hazard identification in this case. This inconsistency and the fact that no other study had detected such an effect has been noted in a response to the original study (Farsalinos, 2017).</p> <p>While recent publications have also recorded the presence of aldehydes in some e-cigarette aerosols, they record aldehydes at levels that are at maximum 100-fold less (Conklin, 2018, Farsalinos, 2018; Sleiman, 2016; Kosmider 2014) than those reported by Khlystov and Samburova, 2016. As the SCHEER opinion notes in the Exposure Assessment (6.5.2, page 38 line 1-2), “The higher carbonyl levels in several studies most probably are generated under dry puff conditions and can be considered unusable for the risk assessment.” As such, this same principle should be applied to section 6.5.3</p> <p>Pg 40, ln 33 – Pg 41, ln 16 considers relevant oxidation products, such as formaldehyde, acetaldehyde and acrolein. This section is very confusing especially in context with the data presented in Table 5 of section 6.5.2. It appears that the intent of presenting the information in this manner is to compare the values for exposure limits to the values found in Table 5. This is misleading. The exposure limits presented in this section are for room air, not per puff exposure limits and this is not adequately explained in this section. While this report includes permissible exposure limits (in units of mg/M3) it does not reference any way to correctly compare these values to the data presented in Table 3 or 5 which are calculated differently. The work by Flora 2016 provides guidance on how to compare permissible exposure limits to e-vapor product yields.</p> <p>We recommend that a pre-section be added to 6.5.3 that addresses how one might convert exposure limits into a daily exposure amount to facilitate a comparison with Table 3. Without this</p>	<p>The reference has been replaced.</p> <p>This paragraph is descriptive, reference to section on Exposure is already given.</p>
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information, the exposure limits have no context or meaning.

A number of quoted studies were uploaded with this submission as either a full .pdf or as a first page .jpg as allowed by the 1MB file limit or copyright rules. Please fully respect copyright rules as described in the upload studies.

147	Vuerich Michela,A NEC, European consumer voice in standardisation,Belgium	6.5.3 Hazard identification of most relevant compounds	Page 46, lines 8-15: it is difficult to understand why substances which have been identified in a huge number of samples according to the Klager et al. and Farsalinos et al. studies referred to on page 30 have not been included in Table 7 (diacetyl, acetoin, acetylpropionyl) and the preceding text. We believe that also some other substances such as benzaldehyde (cherry flavour) which may be present in high concentrations and which are of concern merit inclusion. We would be also concerned about Cd and Ni not included in the table and the preceding text.	See the reply to comment 144.
148	Woessner Julie,International Network of Nicotine Consumer Organisations (INNCO),Swiss based association with 35 orgs all over the world and 15 from the EU	6.5.3 Hazard identification of most relevant compounds	Page 39 / Lines 42-45 We note that this section containing lines 42-45 is making broad assertions as to the unspecified possibilities of cross-reactions between compounds thus creating new compounds, some of which may be hazardous or potentially hazardous. This is overly cautious and generic for almost any physical interaction between humans and the elements. SCHEER refers to “previous section on Exposure” for additional information (which we take to mean Sections 6.5.1 and 6.5.2, and pages 20-39), but the references are not found in any section entitled “Exposure”, so the entire passage (lines 42-45) should ideally be struck in entirety.	This paragraph was revised. The reference to the exposure section This was included to give more information on the generation of the compounds mentioned.
149	Woessner Julie,International Network of Nicotine Consumer Organisations (INNCO), Swiss	6.5.3 Hazard identification of most relevant compounds	Page 40 / Lines 5-12 SCHEER makes conclusive statements as to the toxicity of nicotine itself (“About 60 mg is fatal for humans”) without any included references. Moreover, the number SCHEER used is incorrect. The actual lethal dose of nicotine is likely roughly one order of magnitude higher than the number stated in the opinion. The 60mg lethal dose was cited by a renowned Rudolf Kobert, a pharmacologist in 1906 on the basis of highly dubious self-experiments performed in the mid of the nineteenth century. His excellent reputation as a leading scholar in toxicology has	See replies to comments 112 and 193.

	<p>based association with 35 orgs all over the world and 15 from the EU</p>		<p>apparently led to uncritical acceptance and citation of the 60-mg dose by contemporary fellows and successive researchers. The discrepancy between the 60-mg dose and published cases of nicotine intoxication has been noted previously (Matsushima et al. 1995; Metzler et al. 2005), but nonetheless, this value is still accepted without scrutiny and taken as the basis for worldwide safety regulations of tobacco and other nicotine-containing products.</p> <p>Furthermore, this interpretation is supported in the SCHEER opinion itself (Page 50 lines 43-50) where acute toxicity is cited as 5mg per kilogram in a normal adult, or 320 mg for an 80 kilogram male by the European Chemical Agency’s Committee for Risk Assessment.</p> <p>We ask that SCHEER define various terms used in this and other relevant sections, such as the terms “toxicity” and “acute toxicity”, to make the nomenclature clear. See our comment in TERMINOLOGY.</p> <p>The text should be changed to incorporate definitions and reconcile the different and potentially conflicting standards for nicotine “toxicity”. We suggest that a figure of 0.5 grams of nicotine ingested should be stated in the report to correctly represent the best current understanding of nicotine toxicity in vivo.</p> <p>Ref: How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century (Mayer, 2014) doi:10.1007/s00204-013-1127-0 Nicotine intoxication by e-cigarette liquids: a study of case reports and pathophysiology. Maessen GC, Wijnhoven AM, Neijzen RL, Paulus MC, van Heel DAM, Bomers BHA, Boersma LE, Konya B, van der Heyden MAG. Clin Toxicol (Phila). 2020 Jan;58(1):1-8. doi: 10.1080/15563650.2019.1636994. Epub 2019 Jul 9. PMID: 31286797.</p>	
150	<p>Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss</p>	<p>6.5.3 Hazard identification of most relevant compounds</p>	<p>Page 40 / Lines 13-30</p> <p>SCHEER states, “The nicotine used in e-liquids is extracted from tobacco, and the purity of the extracted nicotine can vary depending upon manufacturer and grade. Nicotine extracts may contain natural impurities such as other tobacco alkaloids, but also degradation products like nicotine-N-oxides, cotinine, normicotine, anatabine, myosmine, anabasine, and β-nicotyrine Flora et al., 2017).” TPD mandates pharmaceutical-grade nicotine be used in the EU, and all e-liquids legally available for retail sale within the EU must first undergo a quality test and receive approved</p>	<p>Small amounts of impurities may be present even in the pharmaceutical grade nicotine.</p> <p>The SCHEER evaluation is related to ingredients of the aerosol from electronic cigarettes.</p>

based
association
with 35
orgs all
over the
world and
15 from
the EU

certification from a designated EU pharmaceutical laboratory prior to their being released on the market. This and the effective product liability regulations in place within the EU offer a comprehensive safety net for maintaining e-liquid standards. We further note that Flora et al. is a US study based on US products not subject to the TPD and, as such, is inapplicable to products marketed in the EU under the TPD.

Page 41, Lines 25-32
We note that industry is responsive to new information about hazards associated with particular flavourings and so, for example, some potentially problematic flavouring ingredients have already been largely eliminated (e.g., cinnamonooids). We further note that TPD affords substantial protections in this regard.

Thank you for the comment.

Page 41, lines 36-38
SCHEER notes that flavorings can stimulate electronic cigarette use, especially among vulnerable populations such as non-smoking adolescents. While flavoring may stimulate vaping eventually among vulnerable populations, it is also important to note that flavours stimulate electronic cigarette use among another important, if not critical, population: adults who smoke. SCHEER needs to recognize that while youth use is important to consider, the impact on adults who smoke and who are able to eliminate or reduce their smoking habit using flavoured e-cigarettes is also critically important.

The SCHEER considered these aspects under 6.7

Page 41 / Lines 38-43
The Brand Equity and marketing considerations discussed in this passage are not within the remit of this opinion and add nothing material to the subject matter. However, it does convey a negative connotation which may impact perception of other statements in an undue fashion. This entire passage should be struck.

This is a descriptive part. The SCHEER does not see any negative connotation.

Page 41 Lines 51-57
SCHEER makes conclusive statements as to properties of menthol as an additive with reference to SCENIHR 2016. The SCHEER text is derived from the SCENIHR text, which SCENIHR text involved tobacco additives, mainly cigarette smoking.

This is a descriptive part. The SCHEER evaluation itself is related to concentrations in the aerosol of electronic cigarettes.

Unless sufficiently substantiating citations have been forgotten or omitted by

SCHEER, in which case they should be specified, the passage should be removed or clearly delineated as taken from combustible cigarette science and that there exists no clear indications of similar effects when vaped. The text should be changed to reflect this and the rationale.

Page 45 lines 40-55

As a brief comment, we would like to note the long-held and often repeated view from consumers organisations regarding issues with plasticisers, namely, plastic packaging contact with e-cigarette vaping liquids is exponentially increased with smaller sized refill containers. With any given type/formulation of plastic, the smaller the bottle, the higher the concentration of plasticisers. In addition, the smaller bottles will generate immense amounts of extra waste, pollution in production and potential release of those chemicals into the environment.

Data are given on measurements of different plasticisers in the e-liquids. However, no plasticisers were detected in the aerosol. Therefore, plasticisers were not considered in the risk assessment.

151 Moiroud Jean, Fédération Interprofessionnelle de la Vape (FIVAPE), France

6.5.3 Hazard identification of most relevant compounds

P. 40, line 10: "... About 60 mg (of nicotine) is fatal for humans." No source(s). This is currently a widely questioned belief. Source : <https://link.springer.com/article/10.1007/s00204-013-1127-0>

See replies to comments 112 and 193.

P. 40, lines 19-29: TNSA comes from tobacco extract not from Pharma Nicotine. Products without tobacco extracts are concerned by TSNA exposure. In Visser et Al (2014), it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."

The SCHEER evaluation is related to chemicals in the aerosol.

P. 41, lines 24-32: here are some evidences that flavours have a relevant contribution to smoking cessation: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

P. 41, lines 34-41: This position "Because the vast range of flavoured e-liquids is attractive to vulnerable consumer groups (e.g., adolescents and young adults), there is a clear need for

This is a descriptive part. The SCHEER evaluation itself is related to concentrations in the aerosol of electronic cigarettes.

regulation. " in Havermans & al.2019, isn't scientifically argued. This sounds like a personal statement of the authors, arguing for a need of regulation using a comparison with flavoured tobacco cigarette which are proven to be addictive and unhealthy. It is not the aim of the study to prove flavour attractiveness in vaping products.

P. 45, lines 40-49 (plasticizers): The source used for the identification of diethyl phthalate and diethylhexyl phthalate in many e-liquids is a study carried out in South Korea on Chinese e-liquids dating from 2012: <https://academic.oup.com/chromsci/article/53/6/841/592614>.

This study deals with e-liquids that are absolutely not representative of the products currently available on the European market.

Data are given on measurements of different plasticisers in the e-liquids. However, no plasticisers were detected in the aerosol. Therefore, plasticisers were not considered in the risk assessment.

The Opinion makes use of information from competent authorities in the Netherlands and Greece, which have compiled lists of most common ingredients of e-liquids (see tables in Annex 2).

152 Compernelle Thomas, British American Tobacco, Belgium

6.5.3 Hazard identification of most relevant compounds

P39, LN47-48: It should be made clear that it is reassuring that for most ingredients no harmonised classification exists, as the review process focusses on compounds of potential concern.

P40, LN10: The statement 60 mg nicotine is a fatal dose has been challenged (1) and should be corrected to reflect current knowledge.

P40, LN13-17: This is not applicable to the current EU market, where the TPD requires the ingredients used to be of high purity and various national standards (2,3) clarify this means using nicotine of pharmaceutical grade purity.

P41, LN25-32: Should clarify that flavours comprise diverse compounds that require case by case risk assessments to justify usage and use levels.

For any statement, the hazard identification aspects should be made explicit, e.g. the importance of GRAS and food additive status

The SCHEER would like to recall that the fact that e-cigarettes ingredients have no available CLP harmonized classification (CLH) doesn't mean that these substances do not have toxic properties. It only means that the toxic endpoint does not require a harmonised classification or no CLH dossier was submitted to ECHA. No changes needed. .

See replies to comments 112 and 193.

Small amounts of impurities may be present even in the pharmaceutical grade nicotine.

The SCHEER evaluation is related to ingredients of the aerosol from electronic cigarettes.

provides assurance of low potential systemic hazards (P41, LN26). For those same compounds that have adequate oral data but are lacking in inhalation toxicity data, clarification that the data gaps are limited to local/portals-of-entry effects and not to a deficiency in knowledge of their overall toxicity profile is appropriate here (P41, LN28). The sentence stating "they may be potentially harmful" (P41, LN29) is true for all substances known to science and adds no real insight. Since the cited reference supporting this statement actually investigated consumer flavour preferences and not flavour toxicity, the sentence should be deleted. The next statement is factually incorrect and should also be deleted (P41, LN29-31). Hutzler et al 2014 was a chemical analysis of 28 e-liquids, not a review of health impact and did not conclude "several e-liquids resulted as potentially allergenic". The paper identified 141 compounds in e-liquids, noting that 7 had been reported as skin sensitizers in cosmetics, but without concentration information, and so it properly refrained from making any statements about the e-liquids.

P41, LN48-57: The assertion that facilitating inhalation could contribute to addictiveness is theoretical and, in any event, not relevant in the EU as the TPD prohibits ingredients that the European Commission believes facilitate inhalation. This should thus be deleted.

P41, LN51-57: recite speculative notions and hypotheses regarding menthol that are extracted from SCENIHR (2016) who cite a 2011 US-FDA TPSAC and a 2013 FDA preliminary menthol report (4,5) as their basis. SCHEER, however, neglects to cite major FDA conclusions that soundly refute these speculative mechanisms, i.e., "menthol in cigarettes is likely not associated with increased or decreased levels of biomarkers of exposure" and "menthol in cigarettes is not associated with an increase in disease risk to the user compared to nonmenthol cigarette smokers" (5). There is no factual evidence to support the speculation that the physiological properties of menthol result in greater exposures or consequent disease or addiction risks for e-cigarette users, but there are numerous publications refuting each aspect of the hypothesis in cigarettes: studies of exposure biomarkers (6-9), disease

141 flavouring substances were identified in 28 different e-liquids available on the market by Hutzler et al. in their publication on *Chemical hazards present in liquids and vapors of electronic cigarettes*.

The authors state that ... "These include some potentially allergenic compounds as for example linalool, cinnamic aldehyde, coumarin and eugenol that should be declared by manufacturers to enable for avoidance by sensitised people."

The wording has been adapted for clarification.

epidemiology (10-12), or addiction/dependence (13).

P41, LN52-53: The statement that an increased sensation of airflow increases lung exposure is false and should be deleted (14-18).



C1R0-6.5.3_Hazard_I
D_References_FINAL.r

153 Compernelle
Thomas, British
American
Tobacco, Belgium

6.5.3 Hazard
identification of
most relevant
compounds

P46, Table 7 purports to summarise hazard information but is inconsistent with the data presented in the report, information summarised by regulatory bodies, and conclusions present in peer-reviewed literature. P24, Table 2 indicates glycerol has no CLP classifications, but P46, Table 7 identifies glycerol as an irritant via various exposure routes. While Table 2 indicates that propylene glycol (PG) is classified as an acute oral toxicant and an eye and skin irritant, Table 7 also identifies PG as an irritant via various exposure routes. These carriers are identified as respiratory tract and GIT mucosa irritants (P46) with a footnote stating “data is scarce” without further explanation regarding the weight of evidence contributing to these hazard identifications. Glycerol and PG have been the subject of numerous toxicological evaluations indicating an abundant body of evidence that, under the conditions of their use, glycerol and PG do not exhibit all the hazards identified in Section 6.5.3.

Glycerol is used in many foods, cosmetics and drug products, including a number of bronchioinhalants up to 5% of the formulation (1). In a comprehensive review, glycerol was determined to not be a dermal or ocular irritant (2,3). Additionally, glycerol is of low acute oral toxicity and an EFSA Panel considered that local irritating effects in the GI tract reported in some gavage studies in rat and dogs were likely caused by hygroscopic and osmotic effects of the large bolus doses administered (4). Glycerol is also a natural component of the human body, comprising ~1% of body weight. It is readily metabolized to CO₂ and glucose, which is subsequently incorporated as liver glycogen through normal metabolic processes (4). The combined influences of the large quantities of endogenous glycerol and its very rapid metabolism and clearance have been shown to render measurement of

SCHEER would like to highlight that the toxicity and adverse health effects associated to compounds in electronic cigarettes e-liquids/aerosol (subject to inhalation) - as indicated in table 7 – reflect the outcome of animal testing and/or human studies through inhalation (or dermal) routes of exposure which are relevant for the risk assessment in question.

In relation to carriers e.g. glycerol/PG, we would like to clarify that indeed most of the toxicological reviews made by reference bodies relate to hazards and risks associated to oral exposure (solvents in food additives) and can hardly be extrapolated to inhalation (or dermal) routes.

However, in relation to propylene glycol (PG) there is scientific evidence (human and animal studies) showing some irritancy towards the respiratory tract, as submitted in the CLH report and assessed by RAC (2016). In spite of not meeting the CLP criteria for respiratory irritation hazard classification, there were respiratory irritation effects seen in studies under single and repeated exposure.

biomarkers of stable isotope-labeled glycerol delivered from e-cigarette use difficult or impossible to quantify (5). These diverse approvals for use in foods, cosmetics and pharmaceuticals along with its rapid disposition and elimination are all consistent with a very low order of toxicity and none are consistent with an expectation it could have any meaningful irritation of eyes, respiratory tract or GI mucosa.

PG has broad uses in pharmaceutical and consumer products, and as an inactive ingredient in drug formulations. It is used to absorb extra water and maintain moisture in certain medicines, cosmetics and food products. It is a solvent for food colors and flavors and is used as a pharmaceutical excipient in several dosage forms, including as a co-solvent in inhaled aerosols (10-25%) (1,6). The EFSA Panel on Food Additives and Nutrient Sources added to Food reaffirmed an ADI of 25 mg/kg bw/day and indicated that PG was of low irritant potency (6). In 2018, Dalton et al. assessed the potential human toxicity of acute PG inhalation exposure in 10 men and 10 women exposed for 4 hours at 100 mg/m³ and 30 minutes at 200 mg/m³ to PG aerosols (7). Objective measures evaluated included ocular irritation via eye blink task and eye photography and pulmonary function via spirometry. Subjective measures included health symptoms ratings, irritation and dryness ratings of eyes, nose, throat and mouth. No respiratory or ocular effects were observed, leading the authors to conclude that, at concentrations tested, PG does not affect respiratory function or produce ocular irritation (7).

These diverse approvals for use in foods, consumer products and pharmaceuticals and human clinical data are all consistent with a very low order of toxicity for PG and none are consistent with an expectation that it have any meaningful irritation of the eyes, respiratory tract or GI mucosa.

Ref:

US Food and Drug Administration (FDA). Inactive ingredient search for approved drug products. Rockville, MD. Accessed at <https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>; 2020.

Becker LC, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, et al. Safety assessment of glycerin as used in cosmetics. *International Journal of Toxicology*. 2019; 38(3_suppl):6S-22S.

		<p>Cosmetic Ingredient Review Expert Panel. Safety Assessment of Glycerin as Used in Cosmetics. 2015. Accessed via https://online.personalcarecouncil.org/ctfastatic/online/lists/cir-pdfs/FR679.pdf.</p> <p>EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Mortensen A, Aguilar F, Crebelli R, Di Domenico A, Dusemund B, et al. Re-evaluation of glycerol (E 422) as a food additive. EFSA Journal. 2017; 15(3):4720, 64 pp.</p> <p>Landmesser A, Scherer M, Pluym N, Sarkar M, Edmiston J, Niessner R, Scherer G. Biomarkers of exposure specific to e-vapor products based on stableisotope labeled ingredients. Nicotine & Tobacco Research. 2018; 21(3):314-322.</p> <p>EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS), Younes M, Aggett P, Aguilar F, Crebelli R, Dusemund B, et al. Scientific Opinion on the re-evaluation of propane1,2-diol (E 1520) as a food additive. EFSA Journal. 2018; 16(4):5235, 40 pp.</p> <p>Dalton P, Soreth B, Maute C, Novaleski C, Banton M. Lack of respiratory and ocular effects following acute propylene glycol exposure in healthy humans. Inhalation Toxicology. 2018; 30(3):124-132.</p>	
<p>154</p>	<p>No agreement to disclose personal data</p> <p>6.5.3 Hazard identification of most relevant compounds</p>	<p>P.39, 145: The document cited by Khlystov and Samburova is not representative of the current state of the art. Dr. Konstantinos Farsalinos, an eminent researcher on electronic cigarettes, wrote a letter (doc. 17) to the editor of the journal pointing out some of the problems: the document is not consistent with similar studies and should not be used as a basis for the SCHEER report. We enclose a number of more representative studies: for instance, Conklin et al (2018) (doc. 18) and Farsalinos et al (2018) (doc. 19) both found little or no increase in aldehyde content compared to unflavoured electronic cigarette fluid. Also, it should be noted in this context that, according to the WHO, ambient air contains between 10 and 200 µg / m3 of formaldehyde (doc. 20).</p> <p>p.40, 130: The report discusses the carcinogenic potential of nicotine based on the presence of trace N-nitrosamines in nicotine preparations derived from tobacco, including those used in the pharmaceutical industry to produce nicotine replacement therapies. Since electronic cigarettes are manufactured using pharmaceutical grade nicotine, these substances are hardly detectable in the e-liquids. A 2020 study found out that electronic cigarettes contain negligible levels of nitrosamines (doc. 21).</p> <p>P.41, 116: Flora et al (2015) provides guidance on how to compare allowed exposure limits. Burstyn (2013) is mentioned among the quotes, without appearing in the text of the report. This study</p>	<p>Based on this comment, this paragraph was revised. The reference has been replaced.</p> <p>Small amounts of impurities may be present even in the pharmaceutical grade nicotine.</p> <p>The SCHEER evaluation is related to ingredients of the aerosol from electronic cigarettes.</p> <p>The reference to Flora et al. (2017) has been deleted.</p>

carried out an assessment of toxic exposures to electronic cigarettes compared to the "total limit values" (TLVs) for occupational health-related exposures. Burstyn concluded that: "The vast majority of predicted exposures are <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was possible".

Ref:

Conklin et al (2018). Electronic cigarette-generated aldehydes: The contribution of e-liquid components to their formation and the use of urinary aldehyde metabolites as biomarkers of exposure. *Aerosol Sci Technol* . 2018 ; 52(11): 1219–1232. doi:10.1080/02786826.2018.1500013.

Farsalinos et al (2018). Aldehyde levels in e-cigarette aerosol: Findings from a replication study and from use of a new-generation device. *Food Chem Toxicol*. 2018 Jan;111:64-70. doi:10.1016/j.fct.2017.11.002.

WHO. (2010). WHO guidelines for indoor air quality: selected pollutants.

Belushkin et al (2020). Selected Harmful and Potentially Harmful Constituents Levels in Commercial e-Cigarettes. *Chem. Res. Toxicol*. 2020, 33, 657–668. DOI:10.1021/acs.chemrestox.9b00470

Farsalinos et al (2017). Comment on "Flavoring Compounds Dominate Toxic Aldehyde Production during E Cigarette Vaping" DOI:10.1021/acs.est.6b06030 *Environ. Sci. Technol*. 2017, 51, 2491–2492

The Burstyn study was not included in the final Opinion: see answer to Comment 89.

155	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.3 Hazard identification of most relevant compounds	Pge 45, lines 40-55 Please consider that there is no reference to any concerns regarding substances that may leach from the product containers despite this section on plasticizers.						Data are given on measurements of different plasticisers in the e-liquids. However, no plasticisers were detected in the aerosol. Therefore, plasticisers were not considered in the risk assessment.
156	Ciprian Boboi, Asociația Industriei de Vaping (Vaping Industry Association), Romania	6.5.3 Hazard identification of most relevant compounds	P	39/ 40/ 40	L	34 19 41/	-	45 30 16	See reply to comment 157.
			 Hazard_identification_of_most_relevant_co						
157	Ciprian Boboi, Asociația Industriei	6.5.3 Hazard identification of most relevant compounds	Line	P 39;	L	34	-	45	The cited paper by Khlystov and Samburova does not represent current science. Dr. Konstantinos Farsalinos, a prominent
									The reference has been replaced.

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n),Romani
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researcher of e-cigarettes, wrote a letter (*1) to the editor of the journal pointing out some of the issues with this manuscript. The paper is not consistent with other similar studies and should not be used as a basis for the SCHEER report. We attach a number of studies that are more representative of the current consensus: Conklin et al (2018) (*2) and Farsalinos et al (2018) (*3) both found small or zero increases in aldehyde content compared with non-flavored e-cigarette liquid; these studies should be cited. It should be noted in this context that according to the WHO (*4), ambient air contains between 10 and 200 µg/m³ of formaldehyde.

P 40; L 19 - 30
The report discusses the cancerogenic potential of nicotine-based on the presence of N-nitrosamines in trace amounts in tobacco-derived nicotine preparations, including those used in the pharmaceutical industry for the manufacture of nicotine replacement therapies. As e-cigarettes are made using pharmaceutical grade nicotine, these compounds are barely detectable in e-cigarette liquids. Belushkin et al (2020) (*5), for example, tested a wide range of e-cigarettes, all of which contained negligible levels of nitrosamines.

P 40 - 41; L 33 - 16
Flora et al (2015) (*6) provides guidance on how to compare permissible exposure limits to e-vapor product yields. We attach the study “Characterization of potential impurities and degradation products in electronic cigarette formulations and aerosols” and the equation used by the research team. Burstyn (2013) is listed among the citations but does not appear in the text of the report. This study made an early assessment of e-cigarette toxic exposures relative to ‘total limit values’ (TLV) for occupational health exposures. Burstyn concluded: “The vast majority of predicted exposures are <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was possible.” We suggest that a section be added to 6.5.3 that addresses how one might convert exposure limits into a daily exposure amount to

Please see Table 1, answer 4.

Small amounts of impurities may be present even in the pharmaceutical grade nicotine.

The SCHEER evaluation is related to ingredients of the aerosol from electronic cigarettes.

Please see table 1 answer No 1.

The reference to Flora et al. (2017) has been deleted.

The Burstyn study was not included in the final Opinion: see answer to Comment 89.

facilitate a comparison with permissible exposure limits. Absent this, exposure limits have no context or meaning.

P 41; L 34 - 43
 The Committee has chosen to comment on the use of flavors to make products attractive in this section, despite it being focused on the potential health hazards, indicating that the Committee considers the appeal of e-cigarettes to be a hazard in and of itself. In this respect, the Committee could, in the interests of balance, consider how the existence of an attractive alternative to smoking can be of public health benefit in a Europe where 26% smoke and 700,000 die from smoking-related disease annually. In this context, it is worth noting within the report the potential unintended consequences of seeking to make e-cigarettes less attractive. This is discussed at length by the Royal College of Physicians (2016) (*7) who conclude: "...if [a risk averse] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking"

Ref:

* 1- <https://pubs.acs.org/doi/10.1021/acs.est.6b06030>

* 2- <https://www.sciencedirect.com/science/article/pii/S0273230015301276?via%3Dihub>

* 3- <https://pubmed.ncbi.nlm.nih.gov/29109042/>

* 4- <https://www.ncbi.nlm.nih.gov/books/NBK138711/>

* 5- <https://pubs.acs.org/doi/pdf/10.1021/acs.chemrestox.9b00470>

* 6- <https://www.sciencedirect.com/science/article/pii/S0273230015301276?via%3Dihub>

* 7- <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction>

158 Vickery Alan, private individual, Ireland 6.5.4 Human evidence for health impacts of electronic cigarettes
 Started smoking cigarettes in 1976 and ended in 2015 with the help from vaping. I have been vaping electronic devices since January 2015 when I stopped smoking. I had tried a number of different products over the years with no effect. The biggest effect from vaping was the constant hand to mouth movement that I had been doing for the best part of 40 years. This

This contribution does not include any scientific comments on the SCHEER Opinion.

habit was the one thing missing from all the other stop smoking tools I had used. At the moment I vape 2 flavours, RY4 (A tobacco based flavour) and Strawberry milkshake (fruit based flavour) The fruit based flavour has helped when I wanted a snack or sweets , I would get enough sweetness from the vape that I would not turn to hi suger treats. I am now 5 years of smoking and feeling so much better for it. I have also brought my nicotine levels down from 16mg to a more modest 3mg and I have been on that for more then 4 years.

159 Mayer Bernhard-Michael, Pharmacy & Toxicology, University of Graz, Austria

6.5.4 Human evidence for health impacts of electronic cigarettes

page 47, lines 27-54, cont. page 48, lines 1-39
 The effects of nicotine on the cardiovascular system (slight increases in blood pressure and heart rate, similar to the effects of caffeine) are well established and not a peculiarity of nicotine-containing e-cigarettes. Moreover, the SCHEER should have emphasized that smokers switching to e-cigarettes have consumed nicotine before, rendering potential nicotine effects extraneous for over 95 % of e-cigarette users.

Large epidemiological studies show that nicotine replacement therapy (NRT) doesn't increase cardiovascular risk [1,2]. Since the administration route is irrelevant for systemic effects, the results are equally valid for vaping [3,4]. NRT is recommended to aid cessation of smokers, in Austria even teenagers above 12 years of age, without warnings from cardiovascular risk. The SCHEER and several other public health bodies, including the WHO, appear to assert toxicity of nicotine only if present in non-medicinal products.

page 47, lines 52-54, cont. page 48, line 1
 The SCHEER refers to the hypothesis that nicotine impacts the vasculature "via sympathetic nervous stimulation, as well as endothelial cell dysfunction and oxidative stress," even though a published clinical study showed reversal of smokers' endothelial dysfunction to the level of non-smokers as soon as one month after switching to e-cigarettes [5]. Similarly, significant improvement of smokers' vascular function, including aortic stiffness, was observed four months after switching [6]. Throughout its report, the committee highlights speculative opinion papers, e.g., from the European Heart Network, or questionable animal and in vitro

The comments have been taken into account, but mainly reflect specific, small or underpowered studies showing lack of associations.

studies. At the same time, the SCHEER consistently ignores reliable data obtained with humans. It is hard to believe that excellent clinical studies, which demonstrate a lack of harmful cardiovascular and pulmonary effects of vaping, escaped the SCHEER's careful literature search, indicating cherry-picking of papers confirming the committee's preconceived opinion.

Due to the upload limit, only 4 out of 6 cited papers are attached (#3 - #6). Because of this annoying limit, I have commented - or will comment - elsewhere to other untenable claims of this section: lung disease, second-hand exposure, nicotine poisoning, and explosions, to name a few.

1. Mills et al. *Circulation* 129, 28-41 (2014)
2. Benowitz et al. *JAMA Intern. Med.* 178, 622-631 (2018)
3. Farsalinos et al. *Intern. Emerg. Med.* 11, 85-94 (2016)
4. Farsalinos et al. *Ther. Adv. Chronic Dis.* 10, 2040622319877741 (2019)
5. George et al. *J. Am. Coll. Cardiol.* 74, 3112-3120 (2019)
6. Ikonomidis et al. *Food Chem. Toxicol.* 141, 111389 (2020)

160	Albrecht Hans-Peter, Interessengemeinschaft Elektronisches Dampfen (IG ED), Germany	6.5.4 Human evidence for health impacts of electronic cigarettes	p.47, ll.12-25: Exclusive e-cigarette use has been shown to be associated with reduced levels of respiratory symptoms relative to smoking combustible cigarettes.	The comment was considered but not taken into account in the Opinion because of lack of supporting data.
161	Russell William, None, Other	6.5.4 Human evidence for health impacts of electronic cigarettes	Vaping has saved my life, please don't disregard the accurate vaping studies to remove vaping as an alternative to smoking. Glad that vaping has helped me stop smoking, and will lead to a tobacco free lifestyle.	This contribution does not include any scientific comments to the SCHEER Opinion.
162	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	The SCHEER opinion omits important aspect of the assessment of health impacts of electronic cigarettes - the assessment of the relative risk of using electronic cigarettes compared to smoking - and focuses only on health impacts compared to non-smoking. This approach is very selective and does not reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking and not as a cessation tool.	See Table 1, answer 1.

It is important to highlight that there still is a background confusion regarding the concepts of safety and less harmful. The notion of

safety is a component of pharmacological paraphernalia and of safe care. It cannot be extended to tools such as digital devices: it will never be safe spirits and it cannot be a safe smoking product. In the case of spirits it is the quantity which makes it more or less harmful; as to digital smoke it is the content of delivered and inhaled substances, by a specific device, which makes it more or less harmful and the comparison should be always adopted in case of analogical smoking. The final SCHEER opinion should appropriately reflect the above concepts.

163	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	It is far from being accurate to state that there is a large scientific body of studies on risk of diseases posed by electronic cigarettes' use. The data on toxicity and health effects should be taken into account only if they include a comparison between e-cig and conventional smoke.	The comparison is irrelevant and methodologically not accurate; the wording "large" has been moderated.
164	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	The SCHEER opinion omits important aspect of the assessment of health impacts of electronic cigarettes - the assessment of the relative risk of using electronic cigarettes compared to smoking - and focuses only on health impacts compared to non-smoking. This approach is very selective and does not reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking and not as a cessation tool.	See Table 1, answer 1.
			It is important to highlight that there still is a background confusion regarding the concepts of safety and less harmful. The notion of safety is a component of pharmacological paraphernalia and of safe care. It cannot be extended to tools such as digital devices: it will never be safe spirits and it cannot be a safe smoking product. In the case of spirits it is the quantity which makes it more or less harmful; as to digital smoke it is the content of delivered and inhaled substances, by a specific device, which makes it more or less harmful and the comparison should be always adopted in case of analogical smoking. The final SCHEER opinion should appropriately reflect the above concepts.	
165	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	It is far from being accurate to state that there is a large scientific body of studies on risk of diseases posed by electronic cigarettes' use. The data on toxicity and health effects should be taken into account only if they include a comparison between e-cig and conventional smoke.	See Table 1, answer 1.

166	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>pag. 46, line 20-24</p> <p>The SCHEER opinion omits important aspect of the assessment of health impacts of electronic cigarettes - the assessment of the relative risk of using electronic cigarettes compared to smoking - and focuses only on health impacts compared to non-smoking. This approach is very selective and does not reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking and not as a cessation tool.</p>	See Table 1, answer 1.
			<p>It is important to highlight that there still is a background confusion regarding the concepts of safety and less harmful. The notion of safety is a component of pharmacological paraphernalia and of safe care. It cannot be extended to tools such as digital devices: it will never be safe spirits and it cannot be a safe smoking product. In the case of spirits it is the quantity which makes it more or less harmful; as to digital smoke it is the content of delivered and inhaled substances, by a specific device, which makes it more or less harmful and the comparison should be always adopted in case of analogical smoking. The final SCHEER opinion should appropriately reflect the above concepts.</p>	
167	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>pag. 47, line 3-9</p> <p>It is far from being accurate to state that there is a large scientific body of studies on risk of diseases posed by electronic cigarettes' use. The data on toxicity and health effects should be taken into account only if they include a comparison between e-cig and conventional smoke.</p>	See Table 1, answer 1.
168	Kröger Knut ,Helios Clinic Krefeld, ,Germany	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>6.5.4 Human evidence for health impacts of electronic cigarettes Cardiovascular diseases</p> <p>Page 47, Lines 27 -54</p> <p>Page 48, Line 1 – 46</p> <p>6.5.4 Human evidence for health impacts of electronic cigarettes Cardiovascular diseases</p> <p>The most consistent evidence regarding the effect of electronic cigarettes on human health concerns cardiovascular diseases. In November 2019, the European Heart Network (EHN) published a position document regarding the cardiovascular consequences of electronic cigarette's use. The EHN concluded that there is mixed evidence for the effects of electronic cigarettes on the cardiovascular system from short-term exposure. In particular, it was noted that "while some studies have found a higher risk</p>	<p>Thank you for this comment.</p> <p>The SCHEER agrees that further research is necessary to elucidate the explicit influence of nicotine on arteriosclerosis. This has been highlighted in several parts in the Opinion. The SCHEER is not supporting that all nicotine replacement therapies are toxic and dangerous and should be forbidden, but nicotine is a very important toxin.</p>

compared to smoking combustible tobacco cigarettes, short-term electronic cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes”, whereas, the long-term effects on the cardiovascular system are still unknown due to the lack of relevant data. However, the authors underlined that, despite the fact that there is “no evidence” this should not be interpreted as no effect, and findings from recent studies suggest that use may pose a higher risk than so far assumed. The EHN underlined the need for longitudinal studies to elucidate long-term effects of electronic cigarette use on the cardiovascular system and whether electronic cigarette use is less hazardous to cardiovascular health than conventional cigarette smoking in the longer term. Finally, EHN recommends that health professionals should inform patients and the public of the risks related to electronic cigarette use.

Comment: The EHN report also said:

“But what if the alternative to e-cigarette use is smoking combustible tobacco? The 2018 NASEM report⁴⁰ states that “while e-cigarettes are not without health risks, they are likely to be far less harmful than conventional cigarettes”. According to this report, e-cigarettes contain fewer numbers and lower levels of toxic substances than conventional cigarettes and it concludes that:

- there is conclusive evidence that completely substituting e-cigarettes for conventional cigarettes reduces users’ exposure to many toxicants and carcinogens present in conventional cigarettes.
- there is substantial evidence that completely switching from regular use of conventional cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.”

If one reads the EHN report completely, harm reduction associated with e-cigarette in active smokers are as relevant as risks related to electronic cigarette use in non-smokers.

The United States Food and Drug Administration (FDA) has also highlighted the adverse health impacts of electronic cigarette use (Chen, 2013).

Comment: This is true in 2013 based on the knowledge before 2013. 2020 the FDA has authorized Marketing of IQOS Tobacco Heating System with ‘Reduced Exposure’ Information. Thus, SCHEER Preliminary Opinion on Electronic cigarettes paper simply ignore ongoing developments. <https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information>

See Table 1, answer 1.

Tobacco Heating devices are outside of the scope of the SCHEER’s opinion. See 6.1. Definition: ‘Despite their current variety in shapes and forms, electronic cigarettes are devices used to inhale an aerosol received by heating of a liquid that may contain nicotine and/or other chemicals’.

Nicotine remains a very important toxin present in electronic cigarette. Most of the cardiovascular effects demonstrated in humans are consistent with the known sympathomimetic effects of nicotine.

Comment: If nicotine is “a very important toxin” all nicotine replacement therapies are toxic and dangerous and should be forbidden.

The acute sympathomimetic effect of nicotine containing electronic cigarette can possibly be associated with increased cardiac risk populations with and without known cardiac disease. (Moheimani et al., 2017).

Comment: This becomes true for each nicotine replacement therapies. Regular electronic cigarette use with nicotine containing liquid is associated with a shift towards sympathetic predominance in heart rate and associated variability (Moheimani et al., 2017, Franzen et al., 2018), as well as vascular calcification and impaired vascular function (Babic et al., 2019), leading to prolonged elevated systolic blood pressure (Franzen et al., 2018).

Comment: The reference of Babic et al. 2019 is a narrative review attempts to connect current literature about possible effects of nicotine on the environment of the vasculature to the pathogenesis of vascular calcification, focusing on the tunica media of the vessel wall. The Authors concluded: “There is a growing body of evidence implicating that nicotine alone could impair vascular function and lead to vascular calcification. Further research is necessary to elucidate the explicit influence of nicotine on arteriosclerosis.”

This careful conclusion is made to a fact in the SCHEER Preliminary Opinion on Electronic cigarettes paper, which is obviously an over interpretation.

Nicotine replacement therapy is outside of the scope of the SCHEER’s opinion.

Nicotine replacement therapy is outside of the scope of the SCHEER’s opinion. The Moheimani- study has been excluded from the Opinion.

The study of Babic is correctly cited in the opinion and the section on cardio-vascular effects is concluded as follows: ‘that although the long-term direct cardiovascular effects remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product.’ Which is fully in line with the careful conclusions mentioned.

169	Spina Francesco, private, Italy	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 47 lines 18 to 25</p> <p>The study in the report is outdated. A new study by Mr Polosa proves that COPD can ameliorate by switching to E.cigarette it's a 5 years follow up</p> <p>Tobacco smoking is a major cause of preventable premature mortality worldwide, caused primarily by lung cancer, cardiovascular disease and chronic obstructive pulmonary disease (COPD)</p> <p>In a retrospective analyses of smokers with COPD who had been ‘vaping’ (the acting of inhaling from ECs) routinely for at least 24 months reported no negative effects. Furthermore, the same</p>
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The new study by Polosa et al. was reviewed, but it was not further considered in the Opinion because has nothing to add.

			<p>study found a marked reduction in yearly exacerbations of COPD and overall health status improvements assessed with the COPD assessment tool (CAT) and physical activity assessed using the 6-min walk distance test (6MWT). A subsequent prospective follow up at 3 years of the same cohort of COPD patients using ECs regularly, by the same group of researchers, confirmed that these objective and subjective benefits persist long term. One of the most dangerous thing in COPD is relapse, that is at a very high risk from en ex-smoker, by vaping the benefits are higher and the risk of relapsing nearly non existant. Attached study: https://journals.sagepub.com/doi/full/10.1177/2040622320961617</p>	
170	Martinez Javier, JT International SA, Switzerland	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>P.47, l.27 onwards: Please revise the section, “Cardiovascular diseases”. A significant amount of the scientific literature is omitted. To date, the evidence for effects of e-cigarettes on long-term cardiovascular health in adult smokers who have switched to e-cigarettes is inconclusive. Most electronic cigarette users are former tobacco cigarette smokers, and a number are dual users also. No study has accurately and absolutely quantified prior impact of tobacco cigarette smoking on vascular dysfunction in individual e-cigarette users. There is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function. Please refer to NASEM, concluding, “There is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes.” Please refer to the results of a randomized trial published in 2019 George et al. 2019 pointing to a reduction in various markers of cardiovascular disease risk, i.e., vascular endothelial function, vascular stiffness and resting heart rate, in subjects who switch from smoking to vaping. Other clinical trials indicate a reduction in blood pressure with e-cigarette use in adult smokers switching to e-cigarettes. (D’Ruiz et al. 2017, Farsalinos et al. 2016). See also Polosa et al. 2016, Polosa et al. 2017., Farsalinos et al. 2019.</p> <p>P.48, l. 18-20 Please revise SCHEER’s statement, “Most of the cardiovascular effects demonstrated in humans are consistent with the known sympathomimetic effects of nicotine.” It is unclear to which literature SCHEER refers to in support of this statement. The scientific literature suggests that there is no increased</p>	<p>The mentioned papers were taken into account but were not included in the Opinion because of the lack of statistical power to draw null conclusions.</p>

cardiovascular risk of nicotine exposure in consumers who have no underlying cardiovascular pathology. Please refer to our comprehensive peer-reviewed study of the literature. (Price & Martinez 2020), concluding that “Overall, current studies indicate that the nicotine delivered by e-cigarettes does not increase the risk of cardiovascular events in individuals who do not have any underlying cardiovascular disease.” This is consistent with a public report from the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT), stating: “No data were identified regarding repeated or long-term inhalation exposure to nicotine per se in humans and data on longer term effects of nicotine exposure from ENDS are not currently available.”

P.51, 1.30-42 and P.52, 1.2 Please remove SCHEER’s references to “passive smoking” and amend the sentences related to “passive smoking secondary to electronic cigarettes.” SCHEER use of the word ‘smoke’ in the context of e-cigarettes is misleading and inaccurate. E-cigarette aerosol is qualitatively and quantitatively different compared to cigarette smoke. E-cigarettes do not produce “smoke” as opposed to combustible cigarettes. Unlike conventional tobacco products, passive exposure arising from e-cigarette use is resulting from the exhaled and diluted aerosol of an e-cigarette user. No sidestream aerosol or equivalent is produced by e-cigarettes. Please revise and remove the word “smoke” and replace by the term vapor aerosol to maintain scientific accuracy. SCHEER extensively comments 1.44-49 page 51 on environmental tobacco smoke providing references related to combustible cigarettes, which misleads and undermines the entire section “Health effects related to second-hand exposure to aerosol from electronic cigarettes”. Please remove these references and comments related to environmental tobacco smoke from combustible cigarettes. These comments apply also to lines 43-49 at page 52.

Ref:

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT).

Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

Ruiz (2017) Measurement of cardiovascular and pulmonary function endpoints

Farsalinos (2016) Effect of continuous smoking reduction and abstinence on blood pressure and heart rate Farsalinos (2019) Is e-cigarette use associated with CHD and MI

George (2019). Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes.

[National Academy of sciences engineering and medicine 2018. Public health consequences of e-cigarettes](#)

Polosa 2016. Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes

Polosa 2017. Health impact of e-cigarettes. A prospective 3.5 year study of regular daily users who have never smoked

Price 2020 Cardiovascular carcinogenic and reproductive effects of nicotine exposure 0.52 mb.

171	Glover Marewa, Centre of Research Excellence Indigenous Sovereignty & Smoking, New Zealand	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 49, Line 34 Page 49, Line 35-44 Pg 50, Lines 5-15 I also want to comment on: Section 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use Page 71, Line 33.</p>  <p>COREISS_submission_22_October_2020.pdf</p>	See Table 1, answer 1.
172	Bagdades Evis, Apollonion Hospital, Nicosia, Cyprus, Cyprus	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>In a scientific document is important to capture the totality of the available evidence in order to have an approach that will lead to more conscious/informed decisions.</p> <p>The SCHEER Preliminary Opinion haven't assessed in depth one of the most important aspects of e-cigarettes use, the clinical effects vs. conventional cigarettes. There are several studies which indicate a reduction in respiratory symptoms when switching from smoking to vaping e-cigarettes. An example of these studies have been uploaded ("Dongmei 2018_Association of smoking and electronic cigarette use with wheezing and related respiratory symptoms in adults: cross-sectional results from the Population Assessment of Tobacco and Health (PATH) study, At this study the authors concluded: "Vaping was associated with increased risk of wheezing and related respiratory symptoms. BUT current vapers had lower risk in wheezing and related respiratory symptoms than current smokers or dual users but higher than non-users").</p>	See Table 1, answer 1.
173	Poirson Philippe,S	6.5.4 Human evidence for health impacts of	<p>[p. 46 l. 20] Lack references PHE (2015 – 2020), RCP (2016). The lack of these references does not allow the reader to grasp the risk reduction by vaping in relation to smoking. Remember that</p>	See Table 1, answer 1.

ovape,France	electronic cigarettes	<p>smoking causes millions of premature deaths each year, as well as disabling diseases. A scientific report must not hide these elements of critical importance for public health.</p> <p>[p. 47 l. 28 to p. 48 l. 16] It is not clear whether the report refers to acute effects and notes a lack of long-term data, or whether it claims that these acute effects have chronic consequences. The evidence presented seems to be far from established evidence for chronic consequences beyond a temporary acute-onset arousal effect. Even the opinion of EHN concludes, “there is insufficient evidence to date that e-cigarette use is associated with impairment of cardiac function and risk of heart attack and stroke” (EHN 2019) The SCHEER report should be clearer and provide more robust evidence.</p> <p>[p. 48 l. 18-28] 40 years of hindsight on the use of nicotine gums have dispelled the urban legend of heart attacks linked to their use. It is strange that the SCHEER is replaying this about vaping.</p> <p>[p. 49 l.2-6] Contrary to what the report states, none of the studies presented involve real humans. These are only in vitro studies, whose limitations mean that they can only be preliminary to real studies. This should be made clear to the reader.</p> <p>[p. 49 l. 23] Meta-analysis from Stephens evaluates at 0,4 % cancer risk for lifetime.</p> <p>[p. 51. L. 27] Several studies are missing from this analysis, which must be revised accordingly. For example, Klepeis (2017) show no difference in home air pollution between non-users and vaping users.</p> <p>[p. 52 l. 16-41] This passage is incomprehensible.</p>	<p>The section on acute effects does not imply</p> <ul style="list-style-type: none"> - that long term data is lacking - no claim is made concerning chronic consequences. <p>As stated in the Opinion, the report stated clearly: ‘. However, the authors underlined that, despite the fact that there is “no evidence” this should not be interpreted as no effect, and findings from recent studies suggest that use may pose a higher risk than so far assumed. ‘</p>	
174	Champagnac Maxime,Phode,France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>p48 lines 8-9 "inducing cardiac arrhythmias and elevated blood pressure (Moheimani et al., 2017)"</p> <p>This study is not relevant ,with only 43 parcipants. The control group is biased, (male /female ratio; former smoker ratio 10/16 vs 2/18; period of smoking cessation 2,3years vs 13 years). The cardiovascular effect could be linked to the past cigarettes</p>	This study has been deleted from the final Opinion.

175	Champagnac Maxime,Phode,France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>consumption as there were 10(16) former smoker in the e-cig group and only 2(18) in the control group.</p> <p>p48 lines 30-33 "Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells. Most electronic 31 cigarettes containing nicotine have a basic pH > 9, which seems to enhance the dosage of 32 nicotine delivered (Stepanov and Fujioka, 2015)."</p> <p>A study from 2015 is not recent for a 10 years product old. This recent study should be considered to update the SCheer position https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used What are the results of our review? The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes. // Authors' conclusions: [...]We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.</p>	This is the same comment as 135. Please see the reply to comment 135.
176	Champagnac Maxime,Phode,France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>p48 lines 38-39 "to prolonged elevated systolic blood pressure (Franzen et al., 2018)."</p> <p>Study realised with 24mg/ml nicotine containing products not relevant in Europe for electronic cigarette, but relevant for pharmaceutical products</p>	This study has been deleted from the final Opinion.
177	Champagnac Maxime,Phode,France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>p51 lines 39-42 "Of these, solely a single study which evaluates the effects of regular passive smoking exposure due to electronic cigarettes within the home, demonstrating increased levels of ambient air nicotine and biomarkers of nicotine (Ballbe et al., 2014)."</p> <p>Study not taking in account the third hand exposure to tobacco smokes, the difference can't be attributed to only Electronic cigarettes. The airborne markers were statistically higher in conventional cigarette homes than in e-cigarettes homes (5.7 times higher). However, concentrations of both biomarkers among non-smokers exposed to conventional cigarettes and e-cigarettes' vapour were statistically similar (only 2 and 1.4 times higher, respectively). The levels of airborne nicotine and cotinine</p>	SCHEER agrees with the fact that in passive smoking exposures at home or work, it should be taken into account other source of nicotine contamination within the home or workplace as e-cigarette user are very often former smokers.

			<p>concentrations in the homes with e-cigarette users were higher than control homes (differences statistically significant). Our results show that non-smokers passively exposed to e-cigarettes absorb nicotine.</p> <p>This study was realised at home thus It is important to take in count other source of nicotine contamination within the home as e-cigarette user are very often former smokers (ie third hand tobacco smoke)https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230406/ Pages 47-53: In an Italian sample of 395 ever smokers and ever e-cigarette users, 47.1% reported at least 1 adverse event attributable to e-cigarette use: 19.5% dry cough, 12.0% dry mouth, 7.6% throat or mouth irritation, and 6.8% sore throat (Gallus S, Borroni E, Liu X, et al. Electronic cigarette use among Italian smokers: patterns, settings, and adverse events. Tumori. 2020 Apr 26:300891620915784).</p>	
178	Gallus Silvano, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>The assessment of effects on the cardiovascular effects appears to be relatively well founded.</p> <p>Although the chapter assess human evidence, we are of the opinion that animal studies should be reviewed and considered more extensively, since e-cigarettes have been on the market a relatively short period and thus the human data is likely to be limited.</p> <p>In particular, results from animal studies and humane studies with smoking and snus use where nicotine is important for pregnancy outcomes and effects on the fetus and newborn child should have been described since current knowledge here has significant transfer value.</p> <p>The SCHEER report also refers to a study from the USA (Walley et al 2019), where adolescent e-cigarette users have higher levels of the nicotine degradation product cotinine in urine than smokers; thus there is a need for assessing health effects of nicotine particularly carefully in this context. For example, nicotine measurements in blood / serum / plasma using conventional cigarettes or snus could have been seen in the context of similar</p>	This study has been deleted from the final Opinion.
179	Becher Rune,Norwegian Institute of Public Health,Norway	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>The assessment of effects on the cardiovascular effects appears to be relatively well founded.</p> <p>Although the chapter assess human evidence, we are of the opinion that animal studies should be reviewed and considered more extensively, since e-cigarettes have been on the market a relatively short period and thus the human data is likely to be limited.</p> <p>In particular, results from animal studies and humane studies with smoking and snus use where nicotine is important for pregnancy outcomes and effects on the fetus and newborn child should have been described since current knowledge here has significant transfer value.</p> <p>The SCHEER report also refers to a study from the USA (Walley et al 2019), where adolescent e-cigarette users have higher levels of the nicotine degradation product cotinine in urine than smokers; thus there is a need for assessing health effects of nicotine particularly carefully in this context. For example, nicotine measurements in blood / serum / plasma using conventional cigarettes or snus could have been seen in the context of similar</p>	The Opinion was focused only on human studies as regards health effects.

			<p>data from e-cigarette users and provided a basis for comparisons. This could have been discussed more in depth.</p>	
180	George Jacob, University of Dundee, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>The SHEER preliminary opinion on electronic cigarettes (EC) states that there is strong evidence for the long-term systemic impact of EC on the cardiovascular system. The report extensively quotes the European Heart Network position document which in fact states that the long term impact of EC on the CV system is unknown and that EC use in the short-term is likely to be less harmful to the CV system. The conclusion drawn by this preliminary report is at odds with the report it purports to reference and the literature review on page 47 is selective, of poor quality and concerningly unbalanced. The report fails to acknowledge that there are a significant number of human clinical trials that have demonstrated a beneficial effect of switching from tobacco cigarettes to EC as a harms reduction measure.</p> <p>The “study” quoted on the impacts on blood pressure and heart rate (Qasim et al , 2017) is in fact a review which itself quotes a n=24, single cigarette 5-minute exposure study of TC vs EC study (Vlachopoulos et al 2016). No reasonable conclusion can be drawn by such poor quality evidence and certainly not sufficient to be described as “strong”. The next “evidence” quoted in the document regarding endothelial dysfunction and oxidative stress is a pre-clinical review by Higashi et al which does not mention electronic cigarettes or vaping once. It does however, highlight the dangers of tobacco smoking on these parameters which is universally accepted. The study (Moheimani et al) referenced on sympathetic activation was a small (n=42) cross sectional observational study which was not able to assess dual use or compliance. Up to 50% of EC users are dual users and the inability to disentangle prior or concurrent tobacco smoking effects on vascular function without accounting for compliance or concurrent tobacco use makes drawing conclusions of any sort from such studies difficult.</p> <p>The issue with the quality of data on EC thus far has been that the vast majority of the studies have been small, single exposure acute impact studies. On the contrary to this report, there are now a number of longer term human clinical trials that have demonstrated a beneficial impact on the CV system of switching from tobacco</p>	<p>In the final Opinion there is an acknowledgement that there are a significant number of human clinical trials that have demonstrated a beneficial effect of switching from tobacco cigarettes to EC as a harms reduction measure.</p> <p>The Moheimani- study has been excluded from the Opinion.</p>

cigarettes to EC. D’Ruiz et al (Regul Toxicol Pharmacol 2017) studied 105 smokers who were showed significant reductions in blood pressure and heart rate when switched to EC. George et al published a randomised controlled trial with a parallel preference cohort in 124 smokers and found a significant improvement in vascular endothelial function within 1 month of switching away from tobacco cigarettes (JACC 2019). There was no impact of nicotine seen in this study when comparisons of EC with and without nicotine were analysed. Most researchers would agree that the impact of nicotine on the CV system has not been proven in any long term good quality clinical trial. In fact, the indirect evidence from long-term follow-up of nicotine replacement therapy (Hubbard; Tobacco control 2005) trials suggest that there is negligible long-term adverse impact from nicotine per se. Farsalinos et al demonstrated a statistically significant lowering of blood pressure over 52 weeks after a switch to EC in 145 smokers (Intern Emergency Med 2016)

These large studies now indicate that EC can be considered a harms reduction measure for chronic tobacco smokers. No serious researcher would claim that EC’s are completely safe but there is now good quality evidence that it is comparatively a safer option, from a CV point of view compared to tobacco smoking. This point has been completely missed out in this SHEER report.

181	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 47 Line 13: SCHEER SHOULD QUALIFY ‘TRANSIENT’ AND ANY ‘LONG TERM’ POTENTIAL HEALTH IMPACTS OF VAPING</p> <p>As noted in the 2020 Cochrane Review, commonly reported and acute effects reported by some e-cigarette users are mouth/throat irritation and cough (similar to acute effects report by adult smokers using medical NRT products). These are transient effects that dissipate over time. There is also no clear evidence of harm from nicotine e-cigarettes with up to two years of product use (the longest studies to date in the published literature)[1].</p> <p>P47 L18: SCHEER CITES ONE REFERENCE ON THE ACUTE EFFECTS OF NICOTINE-CONTAINING E-CIGARETTES</p> <p>The short-term effects of nicotine have been extensively researched and there is an abundance of data demonstrating that effects such</p>	In the Opinion the transient effect of acute is mentioned when appropriate.
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as elevated heart rate are transient[2]. SCHEER fails to provide this context.

P47 L20: SCHEER states e-cigarette use is associated with a decrease in oxygen saturation in “healthy” and COPD smokers. It fails to mention, however, that the observed decrease is around 1% or less, and that oxygen saturation levels stay well within the normal, healthy range. Importantly, this cited study lacked a sham control condition. We draw SCHEER’s attention to a recent study assessed health outcomes at 5-year follow up in COPD smokers who transitioned to e-cigarettes. After 5-years of e-cigarette use, objective and subjective COPD outcomes were ameliorated compared to continued smoking, and gained benefits appear to persist long term [3].

See Table 1, answer 1.

P47 L25: The cited research has several methodological limitations, including the small size of the study population, which consisted predominantly of long-term smokers; the remainder being e-cigarette-naïve non-smokers. In the former group, observed effects may be confounded by previous smoking which is not considered. No sham control condition was included.

P54 L52: SCHEER DOES NOT CONSIDER THE CARDIOVASCULAR HEALTH OUTCOMES WHEN ADULT SMOKERS TRANSITION TO E-CIGARETTES
There is an abundance of well conducted research demonstrating e-cigarette use is significantly less harmful on the cardiovascular system compared to tobacco smoking, which the Opinion ignores. On cardiovascular disease, the risks of nicotine in the context of short-term e-cigarette use has been found to be low in healthy users. However, people with established cardiovascular disease may incur some increased risk from using e-cigarettes, but the risk is much less than that of smoking[4]. Clinical studies have shown that when adult smokers transition to e-cigarettes, this does not lead to higher blood pressure or heart rate values[5] with blood pressure reductions particularly apparent in adult smokers with an elevated blood pressure over the long term[6]. Moreover, a 2019 British Heart Foundation -funded clinical study, which was omitted from the Opinion, found long-term adult smokers who transitioned to e-

See Table 1, answer 1.

			<p>cigarettes experienced rapid and significant improvements in vascular health compared to continued smoking. Within one month of transitioning to e-cigarettes, there was a significant improvement in the ability of adult smokers' arteries to dilate, endothelial function, and vascular stiffness compared to continued smoking, with females benefiting most from transitioning[7].</p> <p>P48 L18: ECAUSE E-CIGARETTES DO NOT BURN TOBACCO OR CREATE SMOKE, THE CARCINOGENIC POTENCY OF E-CIGARETTE AEROSOLS IS SUBSTANTIALLY REDUCED COMPARED TO TOBACCO SMOKE</p> <p>High quality e-cigarettes have shown to have substantially reduced carcinogenic potency compared to tobacco smoke, with a comparative cancer risk estimated at <1% [8].</p>	See Table 1, answer 1.
182	O'Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>P47L27-P48L47 The National Academies of Sciences, Engineering, and Medicine (2018), Benowitz and Fraiman (2019), and D'Amario et al. (2019) state that there is no available evidence on cardiovascular risk. Two review teams observe that the assessment of cardiovascular risk is controversial, and risk may be attributed solely to nicotine (MacDonald & Middlekauff, 2019; WHO Study Group on Tobacco Product Regulation, 2019).</p> <p>Farsalinos et al. (2019) conducted a pooled analysis of the 2016 and 2017 National Health Interview Surveys and found no association between ENDS use and myocardial infarction or coronary heart disease.</p> <p>A recently published RCT (N=114) by George et al. (2019) demonstrated that 4 weeks of ENDS substitution for smoking resulted in significant improvements in flow-mediated dilation and decreases in vascular stiffness compared to the cigarette user arm.</p> <p>P49L1-20 A five year (assessments at 12, 24, 48, and 60 months) follow up of medical records of patients with COPD who completely or partially substituted ENDS use for smoking compared 19 ENDS users to 20 controls (Polosa et al., 2020). COPD exacerbations were significantly reduced by approximately 50%. Six-minute walk test results and COPD quality of life</p>	The SCHEER believes that there are moderate level of evidences supporting the harmful effects of RC on CVD. See Table 1, answer 1.

assessment scores (CAT) also improved significantly.

A study (Solinas et al., 2020) evaluated exclusive ENDS users with asthma who had stopped smoking. In a web survey (N=382) 91.6% self-reported no worsening of symptoms from ENDS use. Clinical testing of 10 ENDS users with asthma at baseline, 3 months, and 6 months found a significant increase in asthma symptom control and improvements in AQLQ scores for quality of life.

P49L35-7 The Mark et al. survey did not verify if ENDS ever-use was during pregnancy. Nor did it address non-nicotine use, yet 37% of the participants believed that ENDS did not contain nicotine, which suggests that they may have used ENDS to avoid negative health effects on their fetus from nicotine.

P52L26-31 A ban on flavors may have unintended consequences. In a 2017 US survey of daily ENDS users (N=383 adults, 86% exclusive ENDS users), 38.2% stated they would mix their own flavors if non-tobacco flavors were banned, 19.2% would “find a way to buy” and 9.7% said they would return to smoking (Du et al., 2020). In a 2019 survey of 649 current ENDS users in England who reported using flavored liquids, 1 in 5 said if there were a ban on flavors they would either smoke more tobacco or return to smoking tobacco, and one in 10 said they would make their own flavoured e-liquids (McNeill et al., 2020).

Ref:

Benowitz NL and Fraiman JB (2017) Cardiovascular effects of electronic cigarettes. *Nature Reviews Cardiology* 14(8): 447–456. DOI: 10.1038/nrcardio.2017.36.

Mark KS, Farquhar B, Chisolm MS. et al. Knowledge, attitudes, and practice of electronic cigarette use among pregnant women. *J Addict Med* 2015; 9:266–72. National Academies of Sciences, Engineering, and Medicine. 2018. Public health consequences of e-cigarettes. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24952>

183 Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.5.4 Human evidence for health impacts of electronic cigarettes	P.46-55 We suggest to include analysis of comparative risk of e-cigarettes’ use versus continued smoking. The Opinion focuses on the health impact of e-cigarettes vs non-smoking. It is however important to compare the risk of e-cigarettes’ use with continued smoking, and highlight the large body of evidence showing that those products are less harmful compared to continued smoking. McNeill (2018) states: “The health effects of cleaner nicotine products per se is	See Table 1, answer 1.
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important, but the key comparison should be with smoking as, to our knowledge, no-one in public health is recommending nicotine to never smokers. For smokers, cleaner nicotine delivery systems will be orders of magnitude safer.” (p.58), and “Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking.”(p. 20, 175) and “Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking.” (P.19, 174). With regard to CVD, a recent clinical trial (George 2019) showed significant improvement in vascular health already one month after switching from combustible to e-cigarettes.

P.47 1.3-9
While the Opinion rightly points out the limited amount of studies assessing the impact of e-cigarettes on the risk of diseases, it contradicts itself by stating that a “large body of studies” suggest health risks to the user. The few studies reporting an increased risk of CVD or respiratory disease were not designed to conclude on the health effects of e-cigarettes. Most of them were either too short, had no temporal association or did not account for previous smoking history, and the others assessed the acute effect of e-cigarettes (instead of the chronic impact), hence hindering the prediction of disease development.

P.48 1.18
We suggest avoiding using the word “toxin” for nicotine. The conclusion that “Nicotine remains a very important toxin present in electronic cigarettes” is misleading. While we acknowledge that nicotine is not benign, nicotine is not directly responsible for smoking-related disease, nor considered as carcinogenic, cardiovascular or respiratory toxicant (according to the US FDA (2012), Royal College of Physicians (2016)). A recent Cochrane review (2020) evaluated the effect and safety of using e-cigarettes to help people who smoke achieve long-term smoking abstinence, and concluded (based on the analysis of the most relevant clinical trials) that the overall incidence of serious adverse events was “low across all study arms” and that they did not “detect any clear evidence of harm from nicotine [e-cigarettes]”.

The SCHEER has rephrased the wording in the revised version, to moderate level of evidence.

P.49 1.2-20
 While the evidence on deleterious effects of e-cigarettes is covered, the Opinion fails to summarize the effects of switching from smoking to e-cigarettes or any other studies looking comparatively at respiratory symptoms in e-cigarettes' users vs cigarettes' smokers. There are numerous studies reporting reduction in respiratory symptoms in those switching, e.g. data from the PATH study showed that: “(while) Vaping was associated with increased risk of wheezing and related respiratory symptoms. Current vapers had lower risk in wheezing and related respiratory symptoms than current smokers or dual users but higher than non-users. Both dual use and smoking significantly increased the risk of wheezing and related respiratory symptoms” (Dongmei 2020).

See Table 1, answer 1.

P.52 1.26-28
 The literature presents contradicting evidence for this statement and at the most there isn't strong evidence of a gateway effect, e.g. Etter (2018) concluded that “Despite its weaknesses and scant empirical support, the gateway theory of smoking initiation has had enormous political influence”.

References:
 Dongmei 2020 Association of smoking and ecig use
 Etter 2018 Gateway effects and e-cigarettes
 FDA 2012 Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke
 George 2019 Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes
 Hartmann-Boyce 2020 Cochrane Database of Systematic Reviews
 McNeill 2018 Evidence review of e-cigarettes and heated tobacco products
 UK Royal College of Physicians 2016 Nicotine without smoke

184 Waclaw Michalina, Prawo dla Ludzi (Law for People), Poland

6.5.4 Human evidence for health impacts of electronic cigarettes

The report takes the view that “we don't know everything about the long-term effects” rather than the view that “we don't know anything about the long-term effects.” This is a misconception that e-cigarettes as a relatively young product cannot be tested for long-term effect. attention to the information that we already have, among others:
 • E-liquid aerosols are tiny liquid droplets with a relatively simple chemical composition.
 • There are much less detectable hazardous substances in a vaporization spray and much lower concentrations than in cigarette

The SCHEER does not accept the “we don't know anything about the long-term effects.”, since there are studies on health effects of e-cigarettes on human health.

smoke.

- In more than ten years of use, so far, only minor symptoms and risk indicators have been shown.

More than half of the people participating in our consultations admitted that in the long run the abandonment of smoking traditional cigarettes in favor of vaping had a significant impact on the improvement of health. Among other things, the troublesome cough has disappeared, the condition and well-being have improved.

185	Sweeney Damian,European Tobacco Harm Reduction Advocates, Ireland	6.5.4 Human evidence for health impacts of electronic cigarettes	Page 47 lines 3 to 9. The SCHEER begins this section by stating, incorrectly, that there is a large scientific body of studies suggesting that electronic cigarettes' use can pose various risks to the user. This directly contradicts what was said in the same paragraph on page 46: "The health impacts of electronic cigarette's use are still difficult to be established due to the lack of long-term data from epidemiological studies or clinical trials".	The wording has been rephrased.
186	Sweeney Damian,European Tobacco	6.5.4 Human evidence for health impacts of	Page 47 lines 12 to 25 Minor throat irritation and coughs are common short term, minor side effects that are experienced when switching from smoking to vaping. Hajek et al (2019) reported in their randomised control trial, e-cigarettes vrs NRT, that "65.3% of e-cig users 51.2% of NRT users experienced this minor irritation. However, the e-cig group reported greater declines in the incidence of cough and phlegm production from baseline to 52 weeks than did the nicotine-replacement group." Miler JA, Mayer BM, Hajek P (2016) also concluded that the switch from smoking to vaping was associated with a reduced incidence of self-reported respiratory infections. References: Hajek (2019). A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. Miller (2016). Changes in the Frequency of Airway Infections in Smokers Who Switched To Vaping Results of an Online Survey	Injuries due to burns and explosion. Page 54 lines 43 to 48 The Opinion deems the risk of injury due to battery explosion to be strong but the incidence to be low. Li-on batteries are used in phones, laptops, electric cars and in power packs for power tools.

Harm Reduction Advocates, Ireland	electronic cigarettes	Li-ion batteries can become volatile if they are misused due to overcharging, overstressing, or as a result of poor manufacturing processes. They are used by millions of people every day, yet the instances of explosion and fire are relatively low. This issue is not specific to e-cigarettes.	problems is strong, but the incidence is quite low: only few case reports are available Two issues are clearly stated: - It is noted that burns and explosions are a realistic health concern → there is clear evidence from studies - The incidence is quite low → meaning that the frequency is very low The mandate of the Opinion is not to compare with other types of electronic devices and/or other types of cigarettes.	
		As with so much of this report, there is a failure to compare the risks associated with vaping with the risks associated with the behaviour which vaping is replacing, i.e. smoking combustible cigarettes.		
		Public Health England's 2018 evidence review stated that between 2015 and 2017 there were 3527 fires due to cigarettes and 44 deaths, and in the same timeframe there were 13 fires due to e-cigarettes and no deaths (McNeill et al). The US National Fire Protection Association reported that between 2012 and 2016 there was 18000 fires annually caused by smoking, and just 15 fires caused by e-cigarettes in 2015 (Ahrens, 2019). Vaping is therefore far less of a fire risk than smoking combustible cigarettes		
		References: Gov.uk (2018) Evidence review of e-cigarettes and heated tobacco products 2018: executive summary Ahrens, January 2019 Home Fires Started by Smoking Home Fires Started by Smoking.		
187	Sweeney Damian, European Tobacco Harm Reduction Advocates, Ireland	6.5.4 Human evidence for health impacts of electronic cigarettes	Lung diseases, page 49 lines 1 to 20 The main area of concern in this section is an overreliance of in vitro studies, and the omission of studies that examine the effects of vaping on the whole-body system. These in vitro studies invariably involve mega dosing or submerging cells in e-liquid and recording the results, and are in no way indicative of the real-world effects of e-cigarettes. Numerous important studies that directly address the health impacts of e-cigarettes were omitted from this section, and once again no assessment was made in relation to the health benefits experienced when smokers switched to e-cigarettes. This is the most important factor that should be assessed. Polosa et al (2014) identified 18 smoking asthmatics (10 single users, eight dual users) and found that overall, there were significant improvements in spirometry data, asthma control and AHR.	The mandate of the Opinion is not to compare health effects e-cig use to other cigarettes. In vitro studies (P 49 lines 15-20): it is correct that in vitro studies cannot give all answers in view of potential health effects, but when the endpoints measured are well chosen these studies are an aid in understanding the effects in a whole body system. As mentioned above, the mandate is not an comparison between different types of smoking. Here the Scheer summarises all health effects related to e-cig. The studies mentioned are focussing on harm reduction and not on intrinsic risks of e-cig. In paragraphs 6.6 Role in the initiationof smoking (particularly focusing on young people) 6.7 Roleofelectronic cigarettes in the cessation of traditional tobacco smoking and dual use.

Another study by Polosa (2016) confirmed that EC use ameliorates objective and subjective asthma outcomes and shows that these beneficial effects may persist in the long term. The most significant finding of this study was that the reversal of harm from tobacco smoking in asthma patients was observed.

The importance of e-cig use in addiction (and potential switch to classic cigarettes) and cessation is discussed

A key study relating to e-cigarette use and COPD has just been published by Polosa et al (2020). Presenting findings from a 5-year assessment of COPD patients who had switched to e-cigarettes, the study concludes that “EC use may ameliorate objective and subjective COPD outcomes, and that the benefits gained appear to persist long term. EC use for abstinence and smoking reduction may ameliorate some of the harm resulting from tobacco smoking in COPD patients.” These findings were consistent with findings at 24- and 36-month assessments of the same cohort. Cibella et al (2016) found symptoms of cough/phlegm and shortness of breath disappeared in smokers who had switched from smoking to vaping. Those who abstained from smoking by vaping experienced improvements in respiratory function, suggesting that as e-cigarette use aids smoking cessation, it can help to reverse harms caused to the lungs from smoking.

No change needed

References:

- Polosa (2020). COPD smokers who switched to e-cigarettes health outcomes at 5-year follow up
- Polosa (2014). Effect of Smoking Abstinence and Reduction in Asthmatic Smokers Switching to Electronic Cigarettes Evidence for Harm Reversal
- Cibella (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes
- Polosa (2016). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes

188 Sweeney Damian, European Tobacco Harm Reduction Advocates, Ireland 6.5.4 Human evidence for health impacts of electronic cigarettes

Page 48 lines 41 to 45
 An assessment of the health impacts of e-cigarettes should include comparisons with the effects of smoking. The report fails to do this and has chosen instead to compare health impacts from vaping with non-smokers. The majority of e-cigarette users in the EU are former or current smokers (Farsalinos, K. E., Poulas, K., Voudris, V., and Le Houezec, J. 2016), and so the risks of vaping compared to those from continued smoking should be the focus for a health impact assessment of e-cigarettes.

See Table 1, answer 1.

The assumption made in the Opinion that the cardiovascular effects of nicotine obtained via smoking can also be applied to vaping does not stand to reason. The harms from smoking are due to combustion and not to nicotine. Long term epidemiological studies into using nicotine without combustion, such as in snus and NRT, show that nicotine does not pose any serious long-term risks. Lee (2013) carried out an evaluation of health effects of switching from cigarettes to snus. They concluded that “the findings consistently demonstrate that switching from cigarettes to snus is associated with a clearly lower risk of CVD and cancer than in continuing to smoke. The risk in switchers is no different from that in smokers who quit smoking. The findings are consistent with other evidence that adverse health effects of snus are at most minimal.”

This assumption has been deleted in the final Opinion.

Public Health England has been consistent in their message to smokers about the harm reduction potential of switching from smoking to vaping, and the need for accurate information of the relative risks to be conveyed to the public. In their comprehensive literature review in 2018 they stated that “vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking.” With relation to cardiovascular risk and lung disease in particular they said, “Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking.”

George et al (2019) found significant improvements in cardiovascular health in smokers that had completely switched to e-cigarettes. The conclusion of Benowitz et al (2016), a study cited in this opinion, was that completely substituting e-cigarettes for combustible tobacco would substantially reduce the harms from smoking, and result in a net benefit for cardiovascular health. A further study by Benowitz (2017), also cited in this opinion, came to the same conclusion, stating: “the cardiovascular risk of EC use is likely to be much less than that of cigarette smoking”

Ref:

Benowitz NL and Fraiman JB (2017) Cardiovascular effects of electronic cigarettes. *Nature Reviews Cardiology* 14(8): 447–456. DOI: 10.1038/nrcardio.2017.36.

George (2019). Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes.

			<p>Benowitz, N.L. et al (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use, Trends in Cardiovascular Medicine, 2016.</p> <p>Farsolinos (not published). Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries</p> <p>McNeill 2018 Evidence review of e-cigarettes and heated tobacco products</p> <p>Gov.uk (2018) Evidence review of e-cigarettes and heated tobacco products 2018: executive summary (website)</p> <p>Lee (2013). The effect on health of switching from cigarettes to snus – A review.</p>	
189	Secchi Alberto, Pri vato, Italy	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>there is a very important study by Giulia Veronesi: "e-Cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial" Nicotine & Tobacco Research, Volume 21, Issue 1, January 2019, Pages 119–126, https://doi.org/10.1093/ntr/nty047</p>	See Table 1, answer 1.
190	RICHTER DIMITRI OS, THRO MBOSIS INSTITUT E (ISETAT)-GREECE, Greece	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 47 lines 27-54 Page 48 lines 1-47</p> <p>In a scientific document, it is important to capture the totality of the available evidence in order to have an approach that will lead to more conscious/informed decisions. The assessment of health impact and the associated reduced risk and/or harm compared to conventional cigarettes is not well captured at Cardiovascular Diseases Chapter where conclusions seem to exclude published studies which show reduced risk.</p> <p>a) At “Ikonomidis 2020” study the authors concluded: Switching to electronic cigarette for 4 months has a neutral effect on platelet function while it reduces arterial stiffness and oxidative stress compared to tobacco smoking.</p> <p>b) At “Ikonomidis 2018” study the authors concluded that both conventional-cig and e-cig adversely affect arterial elasticity and oxidative stress burden acutely. However, nicotine-free e-cig resulted in a comparatively smaller increase of arterial stiffness. Moreover, replacement of conventional cigarette by nicotine-containing e-cig resulted in reduced central and brachial SBP, arterial wave reflections, and oxidative stress within 1 month, likely because of the reduction of the smoked conventional cigarettes. These findings suggest that the e-cig may be used in a medically supervised smoking-cessation program.</p> <p>c) at “Hussain 2019” study the authors concluded that Tobacco Cigarettes (TC) smokers, particularly females, demonstrate significant improvement in vascular health within 1 month of</p>	See Table 1, answer 1.

switching from TC to E-Cigarettes (EC). Switching from TC to EC may be considered a harms reduction measure.

Ref:

Ikonomidis (2018). Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette An Acute and Chronic Study.

Ikonomidis (2020). Effects of electronic cigarette on platelet and vascular function after four months of use.

George (2019). Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes.

191	Arffman Päivi, Vapers Finland, Finland	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Lung diseases (page 49, lines 1-20)</p> <p>In addressing this issue, it would be important to mention that studies have also found that switching from smoking to e-cigarettes reduces respiratory infections as well as asthma- and COPD symptoms. By focusing solely on the potential risks without putting them into proportion relative to the risks of smoking, this section risks misleading smokers who, by switching to e-cigarettes, would substantially reduce those risk factors.</p> <p>This is the general problem of this report: given that the user base of e-cigarettes consists primarily of smokers/ex-smokers who use e-cigarettes for smoking reduction or cessation, ignoring the transition from smoking to e-cigarettes use and its benefits to health, the report is basically ignoring the central health effects of the use of e-cigarettes among the main user group of these products.</p> <p>Ref:</p> <p>Polosa R, Morjaria JB, Prosperini U, et al. COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. <i>Therapeutic Advances in Chronic Disease</i>. January 2020. doi:10.1177/2040622320961617</p> <p>Campagna (2016). Respiratory infections and pneumonia: potential benefits of switching from smoking to vaping. <i>Pneumonia (Nathan)</i>. 2016 Apr 12;8:4. doi: 10.1186/s41479-016-0001-2. eCollection 2016.</p> <p>Miller (2016). Changes in the Frequency of Airway Infections in Smokers Who Switched To Vaping Results of an Online Survey</p> <p>Polosa (2016). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes</p> <p>Cibella (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes</p>	<p>The mandate of the Opinion is not to compare health effects e-cig use to other cigarettes.</p> <p>In vitro studies (P 49 lines 15-20): it is correct that in vitro studies cannot give all answers in view of potential health effects, but when the endpoints measured are well chosen these studies are an aid in understanding the effects in a whole body system.</p> <p>As mentioned above, the mandate is not an comparison between different types of smoking. Here the Scheer summarises all health effects related to e-cig. The studies mentioned are focussing on harm reduction and not on intrinsic risks of e-cig.</p> <p>In paragraphs 6.6 Role in the initiation of smoking (particularly focusing on young people) 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use</p> <p>The importance of e-cig use in addiction (and potential switch to classic cigarettes) and cessation is discussed.</p> <p>No change needed.</p>
192	Sweeney Damian, European Tobacco Harm Reduction	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Cardiovascular diseases.</p> <p>Page 47 line 44 to 54. Page 48 line 1 to 16</p> <p>The studies cited in this section that purport to show an increase risk to cardiovascular health have not assessed risks from e-cigarettes use, but harms from smoking and from past smoking history. Chen (2013) reports on 36 events that occurred as far back</p>	<p>The SCHEER has not supported that the harmful effects of e-cigarettes on CVD or human health in general are due to combustion.</p>

Advocates,
Ireland

as 1980, this has no relevance to e-cigarettes as they were not invented at the time. Similarly, the studies by Qasim et al (2017), Vlachopoulos et al (2016), and Antoniewicz et al (2016) report on adverse effects of smoking. Another issue with some of the studies cited in this report is the assessing only of acute effects that disappear in a short time.

Since e-cigarettes do not contain tobacco and there is no combustion involved it stands to reason that those who switch to e-cigarettes will substantially reduce their exposure to the harmful chemicals found in the smoke from combustible tobacco. This is borne out in the evidence from a growing body of high-quality studies, including long term studies conducted over a number of years, which have found significant benefits to smokers who have switched from smoking to using e-cigarettes. As Farsalinos and Polosa said in their 2014 safety evaluation and risk assessment of e-cigarettes, “Due to their unique characteristics, ECs represent a historical opportunity to save millions of lives and significantly reduce the burden of smoking-related diseases worldwide.”

Ref;

Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Therapeutic Advances in Drug Safety 2014,

193 Arffman Päivi, Vapers
Finland, Finland
6.5.4 Human evidence for health impacts of electronic cigarettes

Electronic cigarette nicotine poisonings (page 50, line 25 to page 51, line 25)
Serious cases of nicotine poisoning are extremely rare, and the mentioned lethal dose for adults taken orally (60 mg) is based on suspicious self-experiments in the nineteenth century. In light of current knowledge, the oral lethal dose for adults is significantly higher, >500 mg.

Ref:

Mayer (2014). How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century

See reply to comment 112.

194 No agreement to disclose personal data
6.5.4 Human evidence for health impacts of electronic cigarettes

Page 46-55:
SCHEER’s opinion doesn’t take into consideration the emerging body of evidence related to the concept of harm reduction. It is a well-established approach pioneered in the field of drug addiction treatment and it is based on the assumption that less risky products

See Table 1, answer 1.

could be suitable alternatives for smokers who are not able or willing to quit their health damaging habits. In the Czech Republic alone all leading addictologists and smoking cessation experts support the idea that the harm reduction concept is an effective tool in the fight against smoking. Czech expert society for tobacco addiction treatment recommends in its official guidance document electronic cigarettes as viable alternatives to combustible products. (Society for Tobacco Addiction Treatment, https://www.kardio-cz.cz/data/upload/Doporuceni_pro_lecibu_zavislosti_na_tabaku.pdf?fbclid=IwAR3mo4mRxyVP1HGkQNkZB9KPrkChjSLraGhScnrj6kw8TbyitB6-auXsCd0) These aspects should also be reflected in the overall debate.

Page 52-53, Lines 52-40:
 Electronic cigarettes and injuries due to burns and explosions
 There is a section in the SCHEER's opinion dedicated to electronic cigarettes and injuries due to burns and explosions. Practical experience show that these problems are portrayed in an inaccurate manner and appear misleading. As far as we know, there is not a single serious case of health damaging malfunction of electronic cigarette in the Czech Republic. Most of these cases occurred in the United States. The reason is probably both insufficient regulation of general electronic products and its insufficient enforcement. According to our experience, unauthorized tempering with the devices causes most of these problems. If used correctly, the risk of malfunction is nearing zero. It is not appropriate to regulate any kind of consumer goods based on their incorrect use.

195 Ikonomidis MD,PhD,F ESC. Professor of Cardiology Ignatios, National and Kapodistri an University
 6.5.4 Human evidence for health impacts of electronic cigarettes

PAGE 48: LINE 15-16
 The various pathophysiological pathways, through which electronic cigarettes may affect cardiovascular health, either acutely or after chronic use, are evident in this statement paper. The studies included conclude that e-cigarette use enhances oxidative stress, endothelial dysfunction, and vascular injury and therefore may induce negative cardiovascular effects through these mechanisms.
 Although there is a broad range of evidence for the adverse acute effects of e-cigarettes and their toxic properties on the cardiovascular system including oxidative stress and endothelial

The SCHEER agrees that studies concerning the mid-term and long-term use of e-cigarettes and CVD risk are limited and controversial, and we have already mentioned it in the Opinion.

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dysfunction, studies concerning the mid-term and long-term use of e-cigarettes and CVD risk are limited and controversial. In a recent study Ikonomidis et al., investigated the effects of e-cigarette use on aortic stiffness as assessed by pulse wave velocity and augmentation index, exhaled carbon monoxide (CO) concentration, and oxidative stress as assessed by malondialdehyde plasma concentrations, both acutely and after 1 month of use compared to combustible tobacco use in 70 individuals. In this study, we have shown that both conventional cigarettes and e-cigarettes impair arterial elasticity and increase oxidative stress burden acutely. However, both nicotine-free and nicotine e-cigarettes resulted in a smaller increase in arterial stiffness and oxidative stress as compared to acute conventional cigarette smoking. Moreover, switching from conventional cigarettes to nicotine-containing e-cigarettes resulted in a reduction of central and brachial systolic blood pressure, arterial wave reflections, and oxidative stress within 1 month. This beneficial effect may be attributed to the observed large reduction in inhaled CO, which is produced by the combustible cigarettes but not by e-cigarettes. These findings were also confirmed by a subsequent study by Biondi-Zoccai et al. who also found a smaller increase in oxidative stress markers after acute e-cigarette smoking compared to conventional tobacco smoking. Similar findings have been published by George et al. in 114 smokers who were randomized to e-cigarettes with nicotine or e-cigarettes without nicotine for 1 month. In this study, vascular function was assessed by flow-mediated dilation of the brachial artery and pulse wave velocity. Within 1 month of switching from conventional cigarettes to e-cigarettes, there was a significant improvement in endothelial function and arterial stiffness with the largest improvement seen in women and those who complied best with e-cigarette switch. Indeed, those who complied best and avoided dual use had the lowest CO levels and benefitted the most in terms of improvement in endothelial function. Individuals with CO measurements within the lowest tertile had the greatest gain in vascular function improvement.

Another recent study in healthy subjects evaluated the effects of acute and chronic tobacco cigarette (TC) smoking and electronic cigarette (EC) vaping on FMD. FMD was significantly impaired

after smoking one TC, but not after vaping an equivalent “dose” (estimated by change in plasma nicotine) of an EC.

196	Ikonomidis ,MD,PhD, FESC Ignatios , National and Kapodistri an University of Athens ,Greece	6.5.4 Human evidence for health impacts of electronic cigarettes	PAGE 48 LINES 15-16 (CONTINUED)	<p>Another recent study in healthy subjects evaluated the effects of acute and chronic tobacco cigarette (TC) smoking and electronic cigarette (EC) vaping on FMD. FMD was significantly impaired after smoking one TC, but not after vaping an equivalent “dose” (estimated by change in plasma nicotine) of an EC.</p> <p>Most recently Ikonomidis et al, examined the effects of electronic cigarette on platelet and vascular function after 4 months of use compared to tobacco smoking. Forty smokers without cardiovascular disease were randomized to smoke either conventional cigarettes or an electronic cigarette. After 4 months, continuation of conventional cigarette smoking further impaired platelet function compared to vaping as assessed by Platelet Function Analyzer PFA-100 and Light Transmission Aggregometry, (decline 24.1 vs 9.4%, respectively). Conversely, compared to smoking, vaping resulted in greater reduction of exhaled CO, improvement of PWV and reduction of MDA, a biomarker of oxidative stress. Recently Kelesidis et al published a study evaluating cellular oxidative stress (COS) in circulating immune cells in healthy long-term EC vapers compared with nonsmokers. An increased proportion of innate and adaptive immune cell subtypes has been found in long-term EC vapers and this is in concordance with the finding that they had elevated COS as well. The cellular oxidative stress was lower in long-term EC vapers compared with TC smokers and the authors conclude that additional investigation is needed to clarify whether switching to ECs as part of a harm-reduction strategy for cardiovascular disease is effective. We do agree that future studies are needed to investigate both the long- and short-term effects of e-cigarette exposure on cardiovascular health—and particularly in the youth, as well as the</p>	See Table 1, answer 1.
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effects of various types of e-liquids that contain flavors where data is scarce.

197 Bamberger Claude,Aid uce,France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>p47 L27 and next, Cardiovascular diseases 12 references used to state, p15 L5 3. 1. - Overall assessment for electronic cigarette users : "The overall weight of evidence for risk of long-term systemic effects on the cardiovascular system is strong."</p> <p>#1 "In November 2019, the European Heart Network (EHN) published a position document regarding the cardiovascular consequences of electronic..."Except this opinion paper (not an evidence) states"the long-term effects on the cardiovascular system are still unknown due to the lack of relevant data"</p> <p>#2 (Chen, 2013) : "highlighted the adverse health impacts of electronic cigarette use". This paper reports small number of anecdotal events not even always caused by use, would anybody claim cigarettes are safer because only 36 event occurred since the 1980s according to this? "Since the late 1980s, over 100 AE reports on tobacco products have been submitted to FDA (electronic cigarettes, n = 47; cigarettes, n = 36; smokeless tobacco, n = 14; other tobacco, n = 5)."</p> <p>#3 (Qasim et al., 2017) "detrimental acute effects of electronic cigarette use on cardio-metabolic..." Only references to issues caused by smoking, even notes that NRTs don't present those. Only based on composition and not amount. Only expresses concerns and asks for relevant studies (doesn't seem to note the history of evidence for snus of the absence of those effects when smoke isn't present). "The widespread and increasing usage of e-cigarettes in the United States is concerning because of the lack of studies on the long-term health effects of these devices on biological systems"</p> <p>#4 (Higashi et al., 2009) "endothelial cell dysfunction and oxidative stress similar to that of tobacco smoking". Generic publication, in 2009, about a possible hypothesis. Not an evidence.</p> <p>#5 (Moheimani et al., 2017) "ultimately inducing hypertension..." "Of the 42 participants, [...] the mean age was 27.6 years" Strangely if the acute phenomenon was measured, the "ultimately inducing" chronic hypertension wasn't. If vaping is causal in those CVD in a comparable scale as smoking, with common mechanisms,</p>	<p>The SCHEER agrees that studies concerning the mid-term and long-term use of e-cigarettes and CVD risk are limited and controversial, and we have already mentioned it in the Opinion.</p> <p>The Moheimani- study has been excluded from the Opinion.</p>
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smokers quitting and vaping exclusively (as continuing smoking has such a risk) should have more or less the same fate as other smokers for CVD, especially hypertension and strokes. But they don't in population where hundreds of thousands just in France for example have quit with vaping. Of course it is difficult to assess (avoiding bias), especially when, for example, a publication stating an increased risk had to be retracted as it had to count MI occurring before the smokers quit and start vaping to assess an increase... (isn't that the definition of a weak evidence of risk ?) #6 (Zhang et al., 2018) "nicotine impacts vasculature similarly to conventional tobacco smoking" From the abstract "Notably, the level of harmful components such as volatile organic compounds, tobacco-specific nitrosamines and heavy metals in electronic cigarettes are even higher than in traditional cigarettes" 3 examples, 3 statements proven false by countless serious studies, how this publication came as an argument in a review ? ...follow in another comment

198 Bamberger Claude,Aid uce,France 6.5.4 Human evidence for health impacts of electronic cigarettes

p47 L27 and next, Cardiovascular diseases 12 references used to state, p15 L5 3. 1. - Overall assessment for electronic cigarette users : "The overall weight of evidence for risk of long-term systemic effects on the cardiovascular system is strong." previous ref. commented in another comment (ContributionID 4b10e139-2c3e-41fe-a12c-018d084cd94b) #7 (Vlachopoulos et al., 2016) "arterial stiffness [...] similarly to conventional tobacco smoking" Measures nicotine is a stimulant. Acute effect shown by this study and on smoking subjects! "We studied 24 smokers" They had to compare smoking for 5 minutes to vaping for 30 minutes to have a comparable stimulant effect (cf. also Farsalinos et al. 2014)... on smokers. It could be noted that in Vlachopoulos et al 2003 "Effect of caffeine on aortic elastic properties and wave reflection. Journal of Hypertension: March 2003 - Volume 21 - Issue 3 - p 563-570" (citation and abstract uploaded) The same scientists (like others) show the same effect with coffee. It could be noted that WHO had to remove invented risks from coffee. #8 (Antoniewicz et al., 2016) "rapid surges in the number of

The Opinion has been revised accordingly regarding the health effects of electronic cigarettees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

circulating endothelial progenitor cells". Again, study on smokers and not vapers, again acute effect of possible but not even shown concern. "Sixteen healthy seldom smokers were randomized into two groups either exposed or not exposed to 10 puffs of ECV for 10 min [...] Taken together, these results may represent signs of possible vascular changes after short e-cigarette inhalation. [...] Further studies analyzing potential cardiovascular health effects are critical"

#9 (Farsalinos et al., 2014) "increased cardiac output [...]" Not on that subject, measures the absorption time of nicotine, slower with vaping than with smoking.

#10(Franzen et al., 2018) "shift towards sympathetic predominance [...]" "The peripheral systolic blood pressure rose significantly for approximately 45 minutes after vaping nicotine-containing liquid heart rate remained elevated approximately 45 minutes after vaping an electronic cigarette with nicotine-containing liquid" Except it is not long term (but <1 hour) and the condition of this study are a bit strange : subjects are smokers and not vapers, using 24mg/ml and forced vaping (10 puffs, no nicotine before) after not smoking for 24h. "During the study, smokers who were inexperienced in the use of e-cigarettes were introduced to vaping and trained to use an e-cigarette by an experienced e-cigarette user. All participants had to vape the e-cigarette with a minimum of one puff every 30 seconds for 10 puffs".

#11 (Babic et al., 2019) "vascular calcification and impaired vascular function" "This narrative review attempts to connect current literature about possible effects of nicotine [...] Conclusion [...] nicotine alone could impair vascular function" No proportion, no test in population despite long term snus or NRT users exist, no evidence and especially in those amount when clean evidence exist of the contribution of other compounds in smoke.

#12 (Benowitz et al. 2017) "Cardiovascular effects of electronic cigarettes"

It seems a couple of important quotes are missing before the table 8 : "Furthermore, a meta-analysis of 21 clinical trials found that NRT was not associated with an increased risk of major adverse cardiac events compared with placebo." "Snus did not increase the risk of myocardial infarction or stroke among a cohort of Swedish users [...] Given that the cleanest forms

of smokeless tobacco use, unlike cigarette smoking, are generally not associated with an overall increased risk of myocardial infarction or atherosclerosis, nicotine is unlikely to be a major contributor to cigarette-induced atherosclerosis" Again not what is called a strong evidence.

199	Pranas Serpytis, Vilnius University, Faculty of Medicine, Lithuania	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Pages 46-47</p> <p>The SCHEER opinion focuses only on health impacts compared to non-smoking and does not take into consideration the assessment of the relative risk of using electronic cigarettes compared to smoking. Such focus does not reflect the fact that electronic cigarettes are primarily used as alternatives to smoking. Such focus also omits the evidence demonstrating that electronic cigarettes are less harmful compared to continued smoking. The Public Health England in "Evidence review of e-cigarettes and heated tobacco products 2018" stated: "Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping. It should be noted that this does not mean e-cigarettes are safe." and "Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking." Uploaded: 1. Public Health England, Evidence review of e-cigarettes and heated tobacco products, 2018. 2) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes, 2019.</p>	See Table 1, answer 1.
200	Sebrie Ernesto, Campaign for Tobacco-Free Kids, United States of America	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Please consider the following papers and report related to health effects:</p> <ul style="list-style-type: none"> - In a 2019 review of the evidence on the effects of e-cigarettes on respiratory health, researchers found that, "Studies show measurable adverse biologic effects on organ and cellular health in humans, in animals, and in vitro." The researchers also noted that, "The effects of e-cigarettes have similarities to and important differences from those of cigarettes. Decades of chronic smoking are needed for development of lung diseases such as lung cancer or chronic obstructive pulmonary disease, so the population effects of e-cigarette use may not be apparent until the middle of this century. 	The SCHEER has considered these papers, and mentioned and discussed them in the final Opinion.

We conclude that current knowledge of these effects is insufficient to determine whether the respiratory health effects of e-cigarette are less than those of combustible tobacco products.” Citation: Gotts, J. et al., “What are the respiratory effects of e-cigarettes?” The BMJ, 366:15275, published online September 30, 2019.

- In June 2020, the Thoracic Society of Australia and New Zealand (TSANZ) published a position statement about electronic cigarettes that includes health impacts of EC. A total of 3793 papers were identified and reviewed in April 2019, and a conclusion was finalized in December 2019. The position aligned with the findings of the US National Academies of Sciences, Engineering and Medicine (NASEM) report (2018). Citation: McDonald CF et al. Electronic cigarettes: A position statement from the Thoracic Society of Australia and New Zealand. *Respirology* (2020) 25, 1082–1089

- A 2020 study reviewed human and animal studies published to date and summarized the cardiopulmonary physiological changes caused by EC use. Acute exposure to e-cigarette aerosols in human subjects led to increased blood pressure and heart rate. Chronic exposure to e-cigarette aerosols using animal models caused increased arterial stiffness, vascular endothelial changes, increased angiogenesis, cardiorenal fibrosis and increased atherosclerotic plaque formation. Pulmonary physiology is also affected by e-cigarette aerosol inhalation, with increased airway reactivity, airway obstruction, inflammation and emphysema. Citation: Tsai,MC et al. Effects of e-cigarettes and vaping devices on cardiac and pulmonary physiology. *J Physiol* 2020 Sep 25. Online ahead of print.

Ref:
Gotts (2019). J et al What are the respiratory effects of e-cigarettes BMJ
McDonald et al (2020). Electronic cigarettes A position statement from the Thoracic Respirology

201	Sebrie Ernesto, Campaign for Tobacco-Free	6.5.4 Human evidence for health impacts of electronic cigarettes	Please consider the following papers in your review: - Li D, et al. Association of smoking and e-cig use with wheezing and related respiratory symptoms in adults: cross-sectional results from the PATH study. <i>Tob Control</i> 2020;29:140–147. - Caporale A et al Acute Effects of Electronic Cigarette Aerosol	The SCHEER has considered these papers, and mentioned and discussed them in the final Opinion.
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	Kids, United States of America		Radiology 2019; 293:97–106. - Kuntic et al. Short-term e-cigarette vapour exposure causes vascular oxidative stress and dysfunction evidence for a close connection to brain damage and a key role of the phagocytic NADPH oxidase (NOX-2) European Heart Journal (2020) 41, 2472–2483. - Ween et al. Effects of E-cigarette E-liquid components on bronchial epithelial. Respirology (2020) 25, 620–628.	
202	Dahlmann-Dustin, Germany	6.5.4 Human evidence for health impacts of electronic cigarettes	Line # P 47; L 18 - 25 The Committee cites Palamidis as reporting increases in Heart Rate (HR) after acute 1 hour ad libitum use of an unknown ENDS device containing 11 mg nicotine. Contrary to these results, Cossio et al performed a study of 16 healthy smoking naive participants and reported that there was no significant increase in heart rate (HR) or blood pressure (BP) after acute use of either a 0% or 5.4% nicotine ENDS product. In other studies which have reported increased in HR after acute usage, it was noted that these increases were smaller in comparison to those induced by use of combustible cigarettes (Franzen et al 2018; Szołtysek-Boldys et al 2014; Yan and D’Ruiz 2015). One study found that ENDS users had to use the product for 6x longer to approach the increases in HR and BP observed after smoking one conventional cigarette (Vlachopoulos et al 2016). These acute changes in BP and HR have been shown to be attributed solely to nicotine (Antoniewicz et al 2019; Chaumont et al 2018).	See Table 1, answer 1. The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.
			P 47; L 29 The statement that "the most consistent evidence regarding the effect of electronic cigarettes on human health concerns cardiovascular diseases" is based on the European Heart Network's opinion. However, large clinical studies show that the moderate acute effects of nicotine on heart rate and blood pressure are not associated with increased cardiovascular risk. Mills et al (2014) found "no clear evidence of harm" when they examined the cardiovascular effect of a variety of nicotine replacement therapies; since the nicotine used in e-cigarettes is of the same grade (as specified in the European Pharmacopeia) there is no reason to suspect that the nicotine contained in e-cigarettes	

has a different effect. Benowitz et al (2018) reported findings along similar lines when reviewing the cardiovascular effects of nicotine replacement therapies.

P 48; L 10 - 47

This section, which reviews the potential cardiovascular risks of nicotine use, focuses on the cardiovascular effects of nicotine. However, the long term epidemiological data on nicotine use without smoke - for example through the use of licensed nicotine replacement therapies (which have been on the European market for many decades) - do not indicate that such use results in serious health effects.

In line 10, for instance, attention is drawn to Vlachopoulos et al (2016) on the effects of electronic cigarette use on arterial stiffness, which concludes that e-cigarette use can contribute to aortic stiffness. The same authors undertook a similar study on caffeine which came to similar conclusions on the effects of caffeine on aortic stiffness.

However, this does not mean that there is a clear link between nicotine use and cardiovascular diseases due to routine use of either nicotine or caffeine (see Wilson and Bloom, 2016). The Committee fails to acknowledge that the relevant marker for cardiovascular risks is what happens to the cardiovascular system when smokers switch to e-cigarettes. George et al (2019) examined this in their paper “Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes”. The conclusion is clear: that smokers (and in particular female smokers) “demonstrate significant improvement in vascular health within 1 month of switching from TC to EC”.

P 51; L 27 - 55

The studies that are cited in this section of the Committee’s report are completely unrelated to electronic cigarettes. In fact, they relate only to the exposure that is foreseeable from combustible cigarettes, meaning that the data is of no value in this context. It is surprising that the Committee has chosen to use data related to the exposure to cigarette smoke in its conclusion about emissions from electronic cigarettes.



Human_evidence_for
_health_impacts_of_el

203 Ekblad Mikael,Scientific board of the Tobacco-free Finland 2030 organization, Finland 6.5.4 Human evidence for health impacts of electronic cigarettes 6.5.4 Human evidence for health impacts of electronic cigarettes Please see Table 1, answer 1.

6.5.4 Human evidence for health impacts of electronic cigarettes
While the preliminary SHCEER opinion deserves to be commended on its thorough review of the existing scientific and other literature on e-cigarettes and their safety, it remains somewhat unclear, how well the SCHEER opinion captures all major risks involved, as not all the ingredients are known, flavours, metals and ultrasmall particles are not part of the risk assessment. Flavours are known to significantly affect the toxicity of e-cigarettes (Leigh et al 2016). As e-cigarettes are often used together with conventional tobacco products, it would have been good to include the scientific literature on concomitant use, as there are some indications that dual use may be markedly more harmful than use of either type of the product alone. (for example, Wang et al.2018)

It is obviously even less clear on what bases the e-cigarette produces or importers give their assurance in the notification that the product in question is safe when heated and inhaled.

The scientific opinion brings attention to the type of device, which appears to play a key role in the exposure to chemicals and nicotine. The opinion notes (p. 21) that later generation models can be used at much higher power levels (e.g., >200 W) as compared to most earlier devices (ca. <15 W). In addition, it notes that newest pod-mods contains nicotine salts, which reduce throat irritation and result in high peak levels of nicotine, similar to those of a tobacco cigarette, and enables users to consume higher levels of nicotine compared to the vast majority of other brands. Yet, the device type and power are largely unregulated in EU.

Fetal effects

In the SCHEER Preliminary Opinion on Electronic Cigarettes, the effects on fetal development have been overlooked. In experimental animals, prenatal exposure to nicotine disturbs significantly the development of many important organs, especially the central nervous system, lungs and autonomic neural system (Holbrook et al. 2016, England et al. 2017).

Epidemiological implications about harmful effects of nicotine replacement products on human development also exists (e.g. Dhalwani et al. 2018). During fetal development nicotine exposure alters epigenetic programming, e.g. in lungs and gonads (England et al. 2017), which may be transferred beyond generations and which are regarded as the most probable basis for developmental origin of disease (Knopik et al. 2012).

Exposure to vaping

Exposure to vaping-induced chemicals depends on the device and the voltage used. Regardless of the primary vaping product the e-vape aerosols include harmful chemicals that are carried on in small liquid droplets and spread on surfaces around. Particulate matter at vaping conventions are comparable with levels found in bars and nights clubs where smoking is allowed. (Melström et al 2017; Walley et al. 2019)

The health effects of the secondary and tertiary passive e-vape have been identified as risk factors for inflammatory and cardiovascular diseases in animal models (Eaton et al 2018; Marcham & Springston 2019; Walley et al. 2019), and yet an increased body of evidence with concomitant findings has been presented in abstract level for e-cigarette users, too (Rosenkilde Laursen et al. eERS 2020)

Conclusions

Based on the SCHEER preliminary opinion the following conclusions can be drawn:

- 1.As e-cigarettes are often used together with conventional tobacco products, the health effects of concomitant use deserve more attention in the final SCHEER opinion.
- 2.The existing notification scheme without resources to study the notification information, and even more so the accuracy of the information of the products intended for the market, do not ensure the safety of the e-cigarettes in the market. EU level measures to ensure safety should be considered, and the translation of best practices developed in the EU Joint Action on Tobacco Control 1 to all EU Member States should be precipitated.
- 3.In experimental animal models exposure to nicotine disturbs significantly development of brain, lungs and autonomic nervous

system which per se needs to be taken in caution in assessment of exposure of inhaled nicotine in young e-cigarette users and offsprings of all the e-cigarette users.

4.Exposure to vaping has been identified as a potential risk factor for inflammatory and cardiovascular diseases in animal models. Concomitant scientific evidence from ongoing studies in e-cigarettes users have been presented.



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204	Vuerich Michela, AN EC, European consumer voice in standardisation, Belgium	6.5.4 Human evidence for health impacts of electronic cigarettes	Page 51, lines 21-25: It would be interesting how compliance with child resistance requirements were evaluated for commonly used electronic cigarette refill products given that the TSD does not specify such requirements – neither for refill products nor e-cigarettes. Unfortunately the study is not free of charge.	Risk management is outside of the scope of the SCHEER’s opinion.
205	Olteanu Vlad, Juul Labs Inc., Belgium	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>An understanding of possible health effects of e-cigarettes requires proper assessment of both absolute risk and the risk relative to a relevant comparator, i.e. combustible cigarettes, which e-cigarettes are designed to replace. This did not happen in the SCHEER Opinion. Furthermore, the Opinion fails to report key aspects of much of the primary cited literature, includes 2nd-hand exposure citations to articles about combustible cigarettes rather than e-cigarettes and attributes conclusions to cited papers that were not made.</p> <p>One such example is on page 47, line 13 which states that a sub-population of users experience acute mouth/throat irritation, and cough and cite Polosa 2011 and Palamida 2017. In the original paper, Polosa is careful to point out, however, that these adverse effects are short-lived, decreasing substantially from week 4 onwards. Polosa also points out that adverse effects most commonly reported in trials for drugs for nicotine dependence are totally absent with e-cigarettes in this study.</p> <p>The reliance of review articles and the resulting citation chains</p>	<p>See Table 1, answer 1.</p> <p>Polosa 2011 points to adverse effects / side effects associated with redrawing of nicotine in cessation. These effects (depression, anxiety, insomnia, irritability, hunger, constipation) were absent.</p> <p>In the paragraph p 47 on acute effects the effects related to cessation are not discussed, only acute effects due to e-cig use, without prior cigarette use are discussed.</p> <p>Harm reduction is outside of the scope of the mandate.</p>

appear to have resulted in misinterpretation of absolute risks. One heavily cited paper (Benowitz, 2016) discussed the implications for e-cigarettes in cardiovascular toxicity, and whether it is biologically plausible. The paper actually concludes that population-level benefits could be gained if e-cigarettes replace combustible cigarettes.

Page 48, line 9 suggests that e-cigarettes will result in long-term adverse impacts on vasculature citing a review article by Zhang, 2018. But there is no evidence of that in the cited review. The review reports the thoughts of “Professor Choupo Perk”, which in turn are cited to be a work by Ying Zhang, which in turn is citing the results of another paper which was not accessible at this time (Zhang Y. 2017).

Page 47, line 44 indicates that the US FDA has "highlighted the adverse health impacts of electronic cigarette use" and cites Chen 2013. However, this citation provided is a one-page summary that does not contain any data or references on the health effects of e-cigarettes.

The citation chains highlighted above are improper and found throughout the report (see also, section 6.6 page 66, line 28-30). SCHEER should provide a reference with direct evidence of the claim being made rather than utilising a difficult chain of citations that do not provide the evidence for what SCHEER is proposing. Furthermore, there is no acknowledgment or consideration given for the relative risk compared to cigarettes or health impacts resulting from those who switch. The authors ignore several studies and systematic reviews indicating the individual health benefits gained among those who transition away from combustible cigarettes, (Polosa, 2018, 2016) or population level benefits gained if e-cigarettes completely replace combustible cigarettes (Benowitz, 2016, Levy, 20XX, many others).

Ref:

Benowitz, N.L. et al (2016). Cardiovascular toxicity of nicotine: Implications for electronic cigarette use, Trends in Cardiovascular Medicine, 2016. doi:10.1016/j.tcm.2016.03.001.

Polosa (2016). Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. doi: 10.1186/s12931-016-0481-x.

Levy (2019). Potential deaths averted in USA by replacing cigarettes with e-cigarettes. [http:// dx. doi. org/ 10. 1136/ tobaccocontrol 2017 053759](http://dx.doi.org/10.1136/tobaccocontrol.2017.053759)

The SCHEER has deleted these References from the final Opinion.

			Polosa R, Morjaria JB, Prosperini U, et al. Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. <i>Int J Chron Obstruct Pulmon Dis</i> . 2018; 13:2533-2542. Published 2018 Aug 22. doi:10.2147/COPD.S161138	
206	Sproga Maris, Smoke Free Association of Latvia, Latvia	6.5.4 Human evidence for health impacts of electronic cigarettes	Pages 46-47 The SCHEER's view is not covering an assessment of health impacts of e-cigarettes compared to smoking and focuses only on health impacts compared to non-smoking. That does not reflect the reality – cigarettes are primarily used as alternatives to smoking. Lots of scientific materials demonstrates that e- cigarettes are less harmful compared to cigarette smoking. To name a few - "Evidence review of e-cigarettes and heated tobacco products 2018" commissioned by the Public Health England, mentions that: "Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk so that more smokers are encouraged to make the switch from smoking to vaping. It should be taken into account that this does not mean e-cigarettes are safe." And further: "Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking."	See Table 1, answer 1.
207	Farsalinos Konstantinos, University of Patras, Greece	6.5.4 Human evidence for health impacts of electronic cigarettes	Page 47, line 27 to page 11, line 46 [Cardiovascular diseases] The conclusion that "the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong" is particularly problematic and fundamentally wrong. The main problems are: 1. Lack of consideration that the vast majority of e-cigarette users are smokers and many of them have quit smoking. This has been the most important omission in all sections of the report, and results in failure to perform a proper risk assessment analysis. Former smokers are expected to have health benefits if they switch from smoking to e-cigarette use.	The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly. See Table 1, answer 1.

2. This section presents acute effects studies which have no prognostic value and cannot be used to predict long term effects in the cardiovascular system. Acute elevations in blood pressure, heart rate, aortic stiffness and endothelial function have no clinical significance or prognostic value [1], and have been observed with NRTs, exercise and coffee and tea intake [2-5]. However, some of these factors are established (exercise) or possible (coffee) PROTECTIVE factors against cardiovascular disease. Had a similar approach been followed, exercise and coffee would have been classified as risk factors for cardiovascular disease!

3. All these cardiovascular markers have prognostic significance only when measured under strict resting conditions and when refraining from stimulant intake [6]. A recent study identified rapid (within 4weeks) improvement in vascular function (measured at rest) when switching from smoking to e-cigarette use [7]. Improvements were observed with both nicotine-containing and nicotine-free e-cigarettes, as well as in smokers who did not completely quit smoking but had reduced their cigarette consumption. Similarly, another study found a decrease in arterial stiffness only 1 month after smokers initiated e-cigarette use, despite the fact that only 60% were exclusive e-cigarette users [8].

In conclusion, the overall evidence suggests that there is moderate weight of evidence for cardiovascular benefits for smokers who quit smoking with the use of e-cigarettes while no evidence exists about cardiovascular harm for non-smoking e-cigarette users.

1. Farsalinos KE. Acute vs. chronic effects of e-cigarettes on vascular function. *Eur Heart J*. 2020 Apr 14;41(15):1525.
2. Adamopoulos D, et al. Acute effects of nicotine on arterial stiffness and wave reflection in healthy young non-smokers. *Clin Exp Pharmacol Physiol*. 2009 Aug;36(8):784-9.
3. Lefferts WK, et al. Effects of acute aerobic exercise on arterial stiffness and cerebrovascular pulsatility in adults with and without hypertension. *J Hypertens*. 2018 Aug;36(8):1743-1752.
4. Mahmud A, Feely J. Acute effect of caffeine on arterial stiffness and aortic pressure waveform. *Hypertension*. 2001 Aug;38(2):227-31.
5. Vlachopoulos C, et al. Acute effect of black and green tea on aortic stiffness and wave reflections. *J Am Coll Nutr*. 2006 Jun;25(3):216-23.
6. Laurent S, et al; European Network for Non-invasive Investigation of Large Arteries. Expert consensus document on arterial stiffness: methodological issues and clinical applications. *Eur Heart J*. 2006 Nov;27(21):2588-605.

It is correct that acute effects have no prognostic to predict long term effects in the cardiovascular system Therefore the SCHEER did remove the word adverse. It needs to be mentioned that it is incorrect to compare exercise with chemical induced changes.

The detrimental acute effects of electronic cigarette use on cardio-metabolic features include vascular and cardiac impacts (including effects on blood pressure and heart rate) (Qasim *et al.*, 2017).

The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.

			7. George J, et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. <i>J Am Coll Cardiol.</i> 2019 Dec 24;74(25):3112-3120. 8. Ikonomidis I, et al. Electronic Cigarette Smoking Increases Arterial Stiffness and Oxidative Stress to a Lesser Extent Than a Single Conventional Cigarette: An Acute and Chronic Study. <i>Circulation.</i> 2018 Jan 16;137(3):303-306.	
208	Vuerich Michela, AN EC, European Consumer voice in standardisation, Belgium	6.5.4 Human evidence for health impacts of electronic cigarettes	Page 51, lines 21-25: It would be interesting how compliance with child resistance requirements were evaluated for commonly used electronic cigarette refill products given that the TSD does not specify such requirements – neither for refill products nor e-cigarettes. Unfortunately the study mentioned is not free of charge.	Please see the reply to the comment above.
209	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.5.4 Human evidence for health impacts of electronic cigarettes	SCHEER noted their reluctance to use the term “vaping” due to, among other things, a concern that the word might suggest that e-cigarette use is “healthy.” (See our comment in Terminology.) We respectfully suggest that SCHEER must be just as mindful in using terminology that suggests a degree of harm that is unwarranted. Specifically, this section contains numerous references to the use of electronic cigarettes which implies that vaping is smoking. See our comment in the TERMINOLOGY section. Page 50, lines 5-15 SCHEER discusses the research study by Pham et al. (2020) where the authors concluded that electronic cigarettes as a possible risk factor for mental health should be clarified using future longitudinal studies. SCHEER should note research that explores the far more likely relationship between nicotine use and mental health, namely, that people who have mental health issues often use nicotine to help manage their symptoms. “The high incidence of smoking among psychiatric patients might in part be due to a beneficial effect of nicotine on cognition and/or mood. For example, a growing body of evidence suggests that patients with schizophrenia may derive improvement in some areas of cognitive performance after smoking cigarettes or using a nicotine replacement therapy (NRT)” H.-J. Aubin et al., <i>Neuroscience and Biobehavioral Reviews</i> 36, 2012 (uploaded).	This has been changed in the final Opinion. The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.
			Page 50 / Line 17 Using “electronique cigarette smoke” is misleading. It doesn’t	Editorial changes have been done.

respect SCHEER's own terminology as defined on page 19.
Page 51 / Line 2

Using “passive smoking of electronic cigarettes” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 51 / Lines 30-31

Using “passive smoking secondary to electronic cigarettes use” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 51 / Lines 32

Using “passive smokers” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 51 / Line 37

Using “passive smoking due to electronic cigarettes” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 51 / Lines 40-41

Using “passive smoking exposure due to electronic cigarettes” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 51-51 / Lines 44-43

This whole part refers to passive smoking, it has nothing to do with vaping and cannot be used to assess the risk of vaping.
Page 52 / Lines 5-10

The cited study, Díez-Izquierdo et al (2018) is a systematic review on third hand smoke only. It didn't review any data about vaping.
Page 52 / Lines 43-44

Using “passive smoking secondary to electronic cigarettes use” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 52 / Line 45

Using “passive smoking secondary to electronic cigarettes” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.
Page 52 / Lines 47-48

Using “passive smoking induced by electronic cigarettes use” is misleading. It doesn't respect SCHEER's own terminology as defined on page 19.

Ref:
Aubin (2012). Smoking, quitting, and psychiatric disease: A review.
doi:10.1016/j.neubiorev.2011.06.007

210	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.5.4 Human evidence for health impacts of electronic cigarettes	Page 47 / Lines 28-44 SCHEER cites the European Heart Network, however, SCHEER fails to note that the European Heart Network paper relies heavily on the US NASEM report. This gives the impression that this is European data, but it is not.	The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.
			Page 49 / Lines 1-13 SCHEER's unequivocal conclusion that e-cigarettes have consistently negative impacts on lung function and sufferers of COPD etc., is inconsistent with positive findings from current scientific literature and substantial anecdotal experience.	
			All the research papers selected for assessment in this section have failed to contrast the proportional risk of e-cigarettes in comparison with the lethal pulmonary effects of combustible tobacco. The likelihood of a non-smoking adult suffering from diminished lung function suddenly deciding to take up vaping later in life, given their condition is virtually zero. Chronic lung disorders are generally experienced by older adults, especially long-term smokers. Thus, any observations should be tempered against the increased health risk incurred by a person continuing to smoke compared to switching to e-cigarettes.	See Table 1, answer 1.
			Whilst total cessation of cigarettes without the use of e-cigarettes might be a healthier option for sufferers of lung disorders, for people who find it impossible to quit smoking using alternative nicotine products and switching to e-cigarettes is a markedly safer option.	
			A US study selected by the SCHEER: (Chun et al.,2017) includes a potpourri of negative impacts of e-cigarettes ranging from explosions, youth use, chemical contaminants and 'metal fumes inhaled by welders' which indicates a risk of confirmation bias by the author. The body of the research focuses solely upon results obtained from in vitro studies on epithelial cells which have limited traction in comparison to evaluating the effects of human exposure in short to medium-term clinical control trials.	
			We respectfully draw your attention to the recently published study	

performed over 5-years which focused on the medium term effects of the use of e-cigarettes by patients suffering from COPD. (See Polosa, Morjaria, Ther Adv Chronic Dis 2020, Vol. 11: 1–15, DOI: 10.1177/2040622320961617 10/10/2020)

In a 5-year prospective assessment of respiratory parameters in a cohort of COPD patients who have substantially reduced conventional smoking or achieved abstinence by switching to electronic cigarettes, the authors reported “significant and constant improvements in lung function, CAT scores and 6MWD were reported in the EC user group over the 5-year observation period compared with the reference group ($p < 0.05$).” They concluded, “The present study suggests that EC [e-cigarette] use may ameliorate objective and subjective COPD outcomes, and that the benefits gained appear to persist long term. EC use for abstinence and smoking reduction may ameliorate some of the harm resulting from tobacco smoking in COPD patients.”

Page 49, line 34, SCHEER notes there have been few studies reviewing actual use of e-cigarettes in pregnant women. We bring to SCHEER’s attention a 2018 study with additional data to consider. Bowker et al. BMC Pregnancy and Childbirth (2018) 18:233

<https://doi.org/10.1186/s12884-018-1856-4>

Ref:

Bowker et al (2018). Views on and experiences of electronic cigarettes: a qualitative study of women who are pregnant or have recently given birth. <https://doi.org/10.1186/s12884-018-1856-4>

Polosa et al (2020). COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. <https://doi.org/10.1177/2040622320961617>

211	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO),	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 46 Lines 20-24</p> <p>We question the relevance of the WHO 2016 reference, which was based on data that has not been updated. More relevant would have been referencing the 2019 WHO TobReg report which covers the same area, but with different conclusions.</p> <p>Page 47, line 27 through Page 48, line 16</p> <p>The use of the EHN report here is suspect, as position papers are typically purely political, and the SCHEER report should not use</p>	<p>See table 1, answer 2. The reference has been updated.</p> <p>The SCHEER does not agree that EHN is a political forum, and the reports or position papers are political documents. Their reports are based on extensive literature search and investigation.</p>
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	Swiss based association with 35 orgs all over the world and 15 from the EU	<p>such material as a part of a risk assessment or science review. Rather, they should refer to the underlying material with SCHEER's own conclusions. Aside from this the EHN report is heavily based upon the US NASEM report already used by the SCHEER report.</p> <p>Page 48 Lines 30-39</p> <p>The noted figure of "most e-liquids" having a pH >9 is incompatible with findings in later papers which notes that the mean of pH in typical nicotine containing e-liquids is around 8.5. (See DeVito EE, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. Curr Neuropharmacol. 2018)</p> <p>Page 48 line 11 through page 49 line 20</p> <p>The conclusions about taking evidence from nicotine combined with cigarette smoke, and projecting that to e-cigarettes needs to be consolidated with scientific material gathered on nicotine without the smoke (for instance from the Swedish snus data). Otherwise this projection is liable to be faulty.</p> <p>Ref: DeVito et al (2018). E-cigarettes: impact of e-liquid components and device characteristics on nicotine exposure. Current neuropharmacology. 2018;16(4):438-59. DOI: 10.2174/1570159X15666171016164430</p>	<p>The Opinion has been revised.</p> <p>The SCHEER's risk assessment is based on concentrations in the aerosols.</p>
212	Lowenstein, William, S OS Addictions, France	<p>6.5.4 Human evidence for health impacts of electronic cigarettes</p> <p>page 46, lines 18-24 page 47, line 1-10</p> <p>The Scheer opinion concludes that vaping may have health impacts, without balancing benefits and risks of vaping. Today it is clearly established that smoking creates a very strong dependence. Smoking is the leading avoidable risk factor for cancer and it is estimated that around a third of cancers deaths are linked to smoking. And despite these figures and even if the number of smokers has been decreasing in France, smoking prevalence in France was still 32% in 2018 (adults smoking every day or occasionally).</p> <p>What we see today is that strategies based on prohibition have failed. Even for drugs such as cannabis, we have to face reality and propose strategies to reduce risks where total prohibition and recommendations for abstinence have not succeeded.</p>	See Table 1, answer 1.

Using these devices does not resolve the problem of nicotine addiction but clearly reduces the risks linked to combustion. In its recent report “Vaping in England: an evidence update including mental health and pregnancy, March 2020” Public Health England considers that previous conclusions are still important messages to be delivered: “ Vaping regulated nicotine products has a small fraction of the risks of smoking, but this does not mean it is safe. Smokers should be encouraged to try regulated nicotine vaping products along with smoking cessation medications and behavioural support. This will greatly increase their chances of successfully stopping smoking”. Electronic cigarettes thus appear to be a valuable alternative, with reduced risks, which can help progressively help smokers quit smoking or at least reduce smoking. It is recommended to include these considerations in the risk assessment of vaping.

Reference

McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England. London: Public Health England. <https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march-2020/vaping-in-england-2020-evidence-update-summary#vaping-among-adults>

213	Moiroud Jean, Fédération Interprofessionnelle de la Vape, France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>On cardiovascular diseases: P. 47, lines 27-... (cardiovascular diseases): Regarding the Moheimani tox study (2017) , the conclusion mentions that the study cannot clearly establish a link: "Nonetheless, we cannot confirm causality on the basis of this single, small study; further research into the potential adverse cardiovascular health effects of e-cigarettes is warranted. Furthermore, the study is conducted on a small number of individuals (less than 50).</p> <p>Please take into consideration this article by George et al, 2019, on “Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes”: https://www.onlinejacc.org/content/74/25/3112</p> <p>P. 48, line 9: the study by Moheimani et al., 2017, is not relevant with only 43 participants. The control group is biased (male /female ratio; former smoker ratio 10/16 vs 2/18; period of smoking</p>	<p>The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly. The Moheimani- study has been excluded from the Opinion.</p>
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cessation 2,3years vs 13 years). The cardiovascular effect could be linked to the past cigarettes consumption as there were 10 (out of 16) former smoker in the e-cig group and only 2 (out of 18) in the control group.

P. 48, lines 26-28: the study by Moheimani et al., 2017, is weak and shouldn't be considered on its own as there isn't good control group and it was realised with a very few participants.

P. 48, lines 30-33: a study from 2015 is not recent for a 10 years old product. This study should be considered: https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used

What are the results of our review? The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes. Here are the authors' conclusions: [...]We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.

P. 48, lines 38-39: the study was realised with 24mg/ml nicotine containing products. It is therefore not relevant in Europe.

P. 48, table 8: Incomplete restitution of the source used to list the "cardiovascular effects" of nicotine. Benowitz et al, 2016: <https://www.sciencedirect.com/science/article/abs/pii/S1050173816000530>

Notably in the abstract : "... Studies of nicotine medications and smokeless tobacco indicate that the risks of nicotine without tobacco combustion products (cigarette smoke) are low compared to cigarette smoking, but are still of concern in people with cardiovascular disease. Electronic cigarettes deliver nicotine without combustion of tobacco and appear to pose low-cardiovascular risk, at least with short-term use, in healthy users.'

Ref:

George et al. (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. <https://www.onlinejacc.org/content/74/25/3112>

			<p>Hartmann-Boyce J (2020). Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose? https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stopsmoking-and-do-they-have-any-unwanted-effects-when-used</p> <p>Avino et al. (2018). Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers. https://pubmed.ncbi.nlm.nih.gov/29894873/</p> <p>Matt et al. (2011). Thirdhand Tobacco Smoke: Emerging Evidence and Arguments for a Multidisciplinary Research Agenda. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230406/</p> <p>NFPA's ""Home Fires Started by Smoking"" by Marty Ahrens (2019). https://www.nfpa.org/Newsand-Research/Data-research-and-tools/US-Fire-Problem/Smoking-Materials</p> <p>Electronic Cigarette Explosions and Fires: The 2015 Experience https://www.nfpa.org/media/Files/News-and-Research/Fire-statistics-and-reports/US-Fire-Problem/Firecauses/osecigarettes.ashx?la=en</p>	
214	Moiroud Jean, Fédération Interprofessionnelle de la Vape, France	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>On lung diseases: P. 49, lines 1-20: Chun (2017) is a review based on studies with flawed operating procedures. Exposures of several hours continuously on mice will inevitably give aberrant results. It is the same thing with studies on cells where the physical parameters of vaporization are not realistic (smoking machine most often, regular dry puff surely) and therefore the resulting cellular exposures give results that are not relevant. For Jankowski (2017), it is a review based on publications that date for the most part before 2014 and are therefore not representative of the current market and even less so of the European market (American studies). On health effects related to second-hand exposure to aerosol from electronic cigarettes (p. 51, lines 27-57; p. 52 lines 1-10):</p> <ul style="list-style-type: none"> • It should be highlighted that there are no conclusive data on this part. It is therefore baffling that SCHEER considers the risk “moderate” or “weak to moderate”. • Here are some important reminders regarding second-hand exposure to aerosol (and their differences with second-hand smoke) that need to be considered: <ul style="list-style-type: none"> o The quantity of second-hand vapour emitted is only 15% or less. In comparison, smoking emits around 40% of smoke. Vapers absorb most of the vapour, thus minimizing the risks for passive vapers. o Vaping emissions are considerably less toxic than tobacco emissions. o While vaping, exposure to nicotine is relatively benign and does 	<p>It is correct that the data used in this section (p49 lines 1-20) is a mix of in vitro / animal / human data described in section. This broad approach strengthens the context.</p> <p>In the conclusion (weight of evidence) of the section (p 54 line 55 – p 55 line 1-6) the human data was considered used in the weight of evidence.</p>

not reach a detectable level of concentration.
o Vaping emissions take less than 2 minutes to evaporate in a close space, while tobacco emissions take 20 to 40 minutes to dissipate. In conclusion, the overall weight of evidence of carcinogenic risk for passive vapers is neither “moderate” or “weak to moderate” but negligible.

Avino et al. (2018) found that cancer risk for second-hand smokers are 5 times larger than for second-hand vapers. See article here: <https://pubmed.ncbi.nlm.nih.gov/29894873/>

P. 51, lines 39-42: the airborne markers were statistically higher in conventional cigarette homes than in e-cigarettes homes (5.7 times higher). However, concentrations of both biomarkers among non-smokers exposed to conventional cigarettes and e-cigarettes’ vapour were statistically similar (only 2 and 1.4 times higher, respectively). The levels of airborne nicotine and cotinine concentrations in the homes with e-cigarette users were higher than control homes (differences statistically significant). Our results show that non-smokers passively exposed to e-cigarettes absorb nicotine.

This study was realised at home thus it is important to take in count other source of nicotine contamination within the home as e-cigarette users are very often former smokers (i.e. third-hand tobacco smoke
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230406/>)

On electronic cigarettes and injuries due to burns and explosions (p. 52 lines 51-57; p. 53 lines 1-40):
We urge the SCHEER committee to consider adding some level of comparison to their claims, particularly regarding the important number of fires started by cigarettes.
• Between 2012 and 2016, the US National Fire Protection Association has reported 18,000 home fires in the USA due to smoking products (cigarettes). Source: <https://www.nfpa.org/News-and-Research/Data-research-and-tools/US-Fire-Problem/Smoking-Materials>
• However, the same association has only reported 15 fires in 2015 due to vaping products. Source: <https://www.nfpa.org/>

[/media/Files/News-and-Research/Fire-statistics-and-reports/US-Fire-Problem/Fire-causes/osecigarettes.ashx?la=en](#)

Ref :

George et al. (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. <https://www.onlinejacc.org/content/74/25/3112>

Hartmann-Boyce J (2020). Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose? https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stopsmoking-and-do-they-have-any-unwanted-effects-when-used

Avino et al. (2018). Second-hand aerosol from tobacco and electronic cigarettes: Evaluation of the smoker emission rates and doses and lung cancer risk of passive smokers and vapers. <https://pubmed.ncbi.nlm.nih.gov/29894873/>

Matt et al. (2011). Thirdhand Tobacco Smoke: Emerging Evidence and Arguments for a Multidisciplinary Research Agenda. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230406/>

NFPA's ""Home Fires Started by Smoking"" by Marty Ahrens (2019). <https://www.nfpa.org/Newsand-Research/Data-research-and-tools/US-Fire-Problem/Smoking-Materials>

Electronic Cigarette Explosions and Fires: The 2015 Experience <https://www.nfpa.org/media/Files/News-and-Research/Fire-statistics-and-reports/US-Fire-Problem/Firecauses/osecigarettes.ashx?la=en>

215 Compernelle Thomas, British American Tobacco, Belgium

6.5.4 Human evidence for health impacts of electronic cigarettes

This section on the potential for e-cigarettes to cause cardiovascular disease indicates throughout that more evidence is needed and more specifically, that long-term studies are required. However, short-term and acute effect studies, along with hypothetical speculation, are being used to highlight long-term effects such as endothelial dysfunction, oxidative stress, hypertension and cardiac arrhythmias. In addition, these studies highlight their own limitations, for instance Moheimani et al. (1) could only rely on self-reporting of subjects who were asked not to smoke and indicated the unreliability of data collected on product use. Of note, as most of the people switching to e-cigarettes from smoking combustible cigarettes one must also take into consideration that effects on cardio-vascular health could be a consequence of other underlying diseases (2).

In addition, this section fails to put these potential effects of e-cigarettes in context with combustible cigarette use. There have been reports of improvement in endothelial function and vascular stiffness within one month of switching from smoking combustible cigarettes to e-cigarettes (3,4). Additionally, there are studies that report significant reduction in blood pressure with switching from smoking combustible cigarettes to e-cigarettes (5), while others

The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.

The Moheimani- study has been excluded from the Opinion.

See Table 1, answer 1.

report improvement in pulse wave velocity and reduction in malondialdehyde, an indicator of oxidative stress (6).

Some of the references are outdated (e.g. Chen 2013 (7)), which raises concerns over this information's relevance with regards to current products on the market.

Some statements are not referenced (e.g. P48, LN30-31 "Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells"), incorrect references are used (P48: Farsalinos et al 2014 (8)) and some references do not support the claims being made (P48: Franzen et al 2018 (9)).

Generally, this is not a balanced review of the literature and, in fact for the Benowitz and Burbank 2016 reference (10), only a table of potential diseases associated with nicotine use is included. Yet, this paper should be central to this section as it attempts to show from the current literature where e-cigarettes are in terms of potential cardiovascular disease risk in comparison to smoking combustible cigarettes. It also states: "While people with established CVD might incur some increased risk from e-cigarette use, the risk is certainly much less than that of smoking. If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be substantially reduced and there would likely be a substantial net benefit for cardiovascular health" (10). This aligns with other publications which indicate that although e-cigarettes are not harmless, in terms of the risk continuum they are likely to be less harmful than combustible cigarettes (11,12,13).

Overall, the evidence suggests that chemicals other than nicotine are responsible for the elevated risks of myocardial infarction and stroke in smokers. The beneficial epidemiological CVD risk outcomes of smoking cessation are well known and the use of NRT as a cessation aid does not increase CVD. Therefore, it is unproven that nicotine increases CVD risk, and many regulatory agencies such as FDA and PHE state that it is the toxicants from combusted tobacco, and not nicotine, which is causative of smoking-related diseases (14,15).



C1R0-6.5.4_Evidence
_of_Health_Impacts_R

216 Compernelle
Thomas, British
American
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6.5.4 Human
evidence for
health impacts of
electronic
cigarettes

The FDA recently published the Technical Product Lead (TPL) assessment of an MRTP application. In the TPL summary it classed certain HPHCs according to disease relevant toxicity. In terms of cardiovascular toxicity, Acrolein, benzene and 1,3-butadiene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders will be exposed to with glo relative to cigarette smoke.

See Table 1, answer 1.

Similarly, in terms of respiratory toxicity, Acrolein, acrylonitriles, 1-aminonaphthalene and toluene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders are exposed to with glo relative to cigarette smoke.

Finally, for reproductive toxicity, benzene, 1,3-butadiene, carbon monoxide, ethylene oxide, nicotine and toluene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders are exposed to with glo relative to cigarette smoke.

This Opinion is limited and fails to incorporate a number of publications that indicate that e-cigarettes are not entirely without harmful effects but are likely to be less harmful than combustible cigarettes (2-5).

The Opinion points to strong evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system. However, as is made clear in the Opinion, long-term studies are required to verify this while the report bases its findings mainly on studies on acute effects of e-cigarettes to support this position.

Some statements are not referenced (e.g. P48, LN30-31 “Recent

findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells”), incorrect references are used (P48: Farsalinos et al 2014 (6) and some references do not support the claims being made (P48: Franzen et al 2018 (7)).

Potential lung disease effects are largely attributed to acute in vitro studies, many of which are quite old and have little relevance to modern e-cigarettes. It relies a lot on certain in vitro studies, while ignoring other (e.g. 8, 9). Potential links between observations in in vitro studies and cancer risk are also mentioned, while acknowledging that clinical evidence is lacking.

The section on ENDS use and effects in the oral cavity contains no citations.



C2R0-6.5.4_Evidence
_of_Health_Impacts_R

<p>217 Compernelle Thomas, British American Tobacco, Belgium</p>	<p>6.5.4 Human evidence for health impacts of electronic cigarettes</p>	<p>P47, LN13-25: Acute mouth/throat irritation and cough are mentioned in this report, citing studies that specifically looked at switching from cigarettes to e-cigarettes (1,2). Palamidis also looked at the effects of vaping nicotine-free e-liquids in by non-smokers (2). In both studies, the e-cigarette used were early generation devices. In the Polosa study (1), these effects were greatly diminished by the end of the study (week 24). Palamidis actually notes that their study involved 10 minutes vaping in group of vaping-naive individuals, and the effects could be mitigated by experienced vapers. He also reflected that later-generation devices may have different effects. The lung disease section draws on a mixture of individual studies and review articles. Many of these references conclude that further evidence is needed on long-term effects of e-cigarette usage, and this is mentioned in the report section itself. However, some of the statements do not echo these limitations.</p> <p>For example, P49, LN6 states e-cigarette studies demonstrate that e-cig use triggers increased airflow resistance, citing an old reference (3), and that paper only hypothesises this potential health effect</p>	<p>Polosa 2011 points to adverse effects / side effects associated with redrawing of nicotine in cessation. These effects (depression, anxiety, insomnia, irritability, hunger, constipation) were absent. In the paragraph p 47 on acute effects the effects related to cessation are not discussed, only acute effects due to e-cig use, without prior cigarette use are discussed. As mentioned above, the mandate is not an comparison between different types of smoking. Here the Scheer summarises all health effects related to e-cig. The studies mentioned are focussing on harm reduction and not on intrinsic risks of e-cig. See Table 1, Answer 1.</p>
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from flavouring compounds at the time that had links to this endpoint. P49, LN10 describes increased mucin production in e-cig users, but the referenced study (4) does not have clear information on product use (overall product consumption and whether these were solus/dual users).

P49, LN13 links e-cig use to asthma in adolescents, but the cited reference noted there are no long-term studies to confirm either way (5).

P49, LN15 mentions potential links between observed perturbations in apoptosis/necrosis, inflammatory cytokine expression, and ROS generation by e-cigarettes/e-liquids in in vitro studies and cancer, while acknowledging clinical evidence is lacking. Our in vitro studies on Vype ePen in MucilAir did not indicate many of these pathways are perturbed at the gene level and cytokine release is low, and significantly lower than following cigarette smoke exposure (6,7). Objective comparisons to cigarette smoke exposure are absent from this section.

The section on other health effects begins (P49, LN24) with an investigation of the link between e-cig use and head and neck cancer. The only source cited was a review (8) covering only 18 out of 359 studies. Studies selected were mainly in vitro, and the authors concluded that the evidence to date is unclear and longer term studies and more data are needed to make any strong conclusion.

P50, LN5-15 on mental health effects relies solely on one recently published cross-sectional study (9), in which the direction of association could not be established due to study design.

The section on second-hand exposure effects is very weak on evidence, and P52, LN1-2 even states that 'to date data on the long-term consequences of passive smoking of electronic cigarettes on human health are lacking'. Many studies on passive cigarette smoking are cited, but the relevance of these to e-cigarette second-

The SCHEER does not understand why a study conducted in 2012 is less valid? It is true that the authors of this study did hypothesize on the role of flavours, a point we did not take over in this review.

It is correct that the study of Chen 2019 (p 49 line10) is a review and describes effects reported in different studies – not related to one type of e-cig.

P49 line 13: it is correct the short time use is not mentioned:

P49 line 15: as mentioned in the Opinion the effects of long-term use particularly in relation to lung cancer remain to be determined in epidemiological investigations

In this Opinion no comparison is made to combustional cigarette use.

P49 line 24: this is correct and also clearly state in the text of the Opinion: albeit with a low level of evidence. Moreover, within this context, findings from several investigations reviewed corroborated that electronic cigarette use induces DNA damage via increased oxidative stress, with most profound effects being associated with flavoured e-liquid use (Flach *et al.*, 2019). It is apparent that as the long-term health effects of electronic cigarettes remain for the most part unknown to date, further investigations regarding their impacts upon both pulmonary and other health systems are urgently needed (Klein *et al.*, 2019).

P50, LN5-15: correct. This is also clearly cited in the Opinion And taken into consideration in the weight of evidence

P52, LN1-2: the Opinion has been cited correctly. This is taken into consideration when the weight of evidence was evaluated see p 55 line 7 – 10: In addition, with regard to the respective effects of second-hand exposure of

hand exposure is highly questionable. The section on health effects related to second-hand exposure to aerosol from electronic cigarettes is extremely light on evidence. It cites a study that is currently ongoing but with no published data (10), refers to studies on passive cigarette smoking CVD effects (P51, LN44-52) that are not relevant to e-cigarette second-hand exposures, and states that nothing substantial has been reported for e-cigarette equivalent exposures. Third-hand smoke exposure is also mentioned in the context of e-cigarette equivalent exposure, but again relevance is lacking, and there are no data on long term effects in any case.



C3R0-6.5.4_Evidence_of_Health_Impacts_R

children and adolescents secondary to electronic cigarettes use, the weight of evidence cannot be established as there exists a complete paucity of evidence regarding the acute and long-term effects on cardiovascular and other health outcomes in this group

218 Compernelle Thomas, British American Tobacco, Belgium 6.5.4 Human evidence for health impacts of electronic cigarettes

P53, LN42-52: Safety Gate searches on faulty power adaptors (typically used for all Li-ion rechargeable battery powered devices) using key-word ‘power adaptor’, ‘USB charger’, ‘USB power adaptor’ yielded n= 40, 148 and 15 respectively (n total 203). When searching for ‘battery’ recalls there are 1147 results. Which puts the quoted e-cigarette findings (incidence n = 10) as very low and into context for risk levels due to ‘Electrical appliances and equipment’, where “Hoverboard” product recalls have 56 entries over the same period.
P53, LN53-56: the quoted recalls appear to relate to adaptor failures and not necessarily e-cigarette faults; adaptor failures are general risk for all electronic appliances (see previous comment on adaptor failures).
P54, LN1- 4: the remaining one-off e-cigarette battery failure, although a severe occurrence, is still very low when compared to the Safety Gate searches on power adaptor type (n = 203) and battery recalls (n = 1147) and other lithium rechargeable products (hoverboards n = 56).
P54, LN5-8: the LVD (2014/35/EU) covers health and safety risks on electrical equipment operating with an input or output voltage of between 50 and 1000 V for AC, 75 and 1500 V for DC – e-cigarettes as products are typically 5V DC and fall outside LVD compliance requirements. Accepted that power adaptors would be covered under LVD, EMC, RoHS and eco-design requirements for

Thank you for the information on notifications on unsafe products.

all electronic products (not just e-cigarettes). E-cigarette products are covered directly by the CE marking directives of EMC (2014/30/EU) and RoHS (2011/65/EU) and then by aspects of the General Product Safety Directive (GPSD) (2001/95/EC). GPSD sets out safety requirements for all consumer products being placed on the European market (and allows the use of adjacent standards, such as within the LVD safety standards, to control failure modes and risks), but is not a CE marking Directive.

219	No agreement to disclose personal data	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>P. 47, 128: Regarding cardiovascular benefits in the transition from traditional smoking to electronic cigarettes, reference should be made to the results of the study carried out by the "Division of Molecular and Clinical Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, United Kingdom (doc. 22). In particular, it emerged that smokers who switch to electronic cigarettes, experience relevant improvements in vascular activity and endothelial functions after only 1 month.</p> <p>P.49, 12: The review does not consider the impact on the health of smokers with chronic lung diseases. According to a 2016 study by Prof. Polosa, a significant reduction in COPD relapses was observed in the electronic cigarettes user group with COPD; their mean (\pm DS) decreased from 2.3 (\pm 1) at baseline to 1.8 (\pm 1; $p = 0.002$) and 1.4 (\pm 0.9; $p < 0.001$) in F / su1 and F / su2 respectively (doc. 23). A significant reduction in COPD exacerbations has also been observed in electronic cigarettes consumers who have also smoked traditional cigarettes (i.e. "double users").</p> <p>P.49, 120: The allegations only concern "in vitro" studies, which have been carried out without actual reference to human use. These circumstance has led Li Volti et al (2018) to state that such studies do not replicate normal using conditions and fail to use standardised protocols, thus leading to an overestimation of toxicological effects (doc.24).</p> <p>P. 51, 157: Current evidence clearly shows that air concentrations of potential toxic agents are well below internationally established thresholds in indoor environments. The Committee should consider the following studies: McAuley et al (2012). Comparison of the effects of e-cigarette vapor and cigarette</p>	See Table 1, answer 1.
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smoke on indoor air quality. *Inhalation Toxicology*, 24:12, 850-857, DOI: 10.3109/08958378.2012.724728

O'Connell et al (2015). An Assessment of Indoor Air Quality before, during and after Unrestricted Use of E-Cigarettes in a Small Room. *Int. J. Environ. Res. Public Health* 2015, 12, 4889-4907; doi:10.3390/ijerph120504889

Logue et al (2017). Emissions from Electronic Cigarettes: Assessing Vapers' Intake of Toxic Compounds, Secondhand Exposures, and the Associated Health Impacts. *Environ. Sci. Technol.* 2017, 51, 16, 9271-9279. <https://doi.org/10.1021/acs.est.7b00710>

Liu et al. (2017). Determination of selected chemical levels in room air and on surfaces after the use of cartridge- and tank-based e-vapor products or conventional cigarettes. *Int J Environ Res Public Health* 14(9) doi:10.3390/ijerph14090969

van Drooge et al (2018). Influence of electronic cigarette vaping on the composition of indoor organic pollutants, particles, and exhaled breath of bystanders. *Environ Sci Pollut Res Int.* 2019 Feb;26(5):4654-4666. doi: 10.1007/s11356-018-3975-x.

Schober W, Fembachera L, Frenzena A, Fromme H. Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (IQOS, e-cigarette) in passenger cars. *Int J Hyg Environm Health* 2019; 222: 486-493. <https://doi.org/10.1016/j.ijeh.2019.01.003>

220 Saunders Emily, Broughton Nicotine Services, United Kingdom

6.5.4 Human evidence for health impacts of electronic cigarettes

Page 47, lines 13-25 As reported in the cited paper (Miler, 2016) , please note that switching to EC's has actually been associated with a decrease in respiratory infections. Reductions in smokers cough was also seen to be greater for EC's than NRT and such symptoms of cough and irritation was similar to that found for NRT in Hajek (2019.)

Ref:
Hajek (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. DOI: 10.1056/NEJMoa1808779
Miler (2016). Changes in the Frequency of Airway Infections in Smokers Who Switched To Vaping Results of an Online Survey. DOI: 10.4172/2155-6105.1000290

See Table 1, answer 1.

221 Saunders Emily, Broughton Nicotine Services, United Kingdom

6.5.4 Human evidence for health impacts of electronic cigarettes

Pages 47-48 A number of important papers appear to have been omitted for this section and would be helpful to consider. These papers evaluated several aspects EC use and concluded that the data showed a positive outcome with regards to asthma control and positive spirometry data. Improvement in airway function for smokers switching to EC's and abstaining from smoking was also shown in Cibella et al, 2016

Ref:
Cibella et al (2016). Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)*. 2016 Nov 1;130(21):1929-37. doi: 10.1042/CS20160268. Epub 2016 Aug 19. PMID: 27543458.

See Table 1, answer 1.

			Polosa et al (2016). Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. <i>Discov Med.</i> 2016 Feb;21(114):99-108. PMID: 27011045.	
222	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 47 and 48 Cardiovascular diseases. Cardiovascular risk factors are associated with both smoking and conventional cigarettes but also with the use of e-cigarettes. However, it would be helpful to consider that there are several reviews that support the conclusion that the risk is much less with regards to EC use than for conventional cigarettes. One such paper plainly states that ‘The pooled analysis of the 2016 and 2017 NHIS showed no association between EC use and MI or CHD.’</p> <p>Ref: Farsalinos et al. (2019). Is e-cigarette use associated with coronary heart disease and myocardial infarction? Insights from the 2016 and 2017 national health interview surveys. <i>Therapeutic Advances in Chronic Disease</i> 10: 2040622319877741</p>	See Table 1, answer 1.
223	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 48, lines 12-16 It should be noted that other papers have shown that EPC’s are protective to the cardiovascular system and both prevent and repair vascular damage. In a paper by Farsalinos and Polosa (2017) they specifically state that ‘Based on previous evidence with smoking cessation, an increase in circulating EPC’s should be considered a beneficial effect.’ A paper by George et al (2019) also states that there is an improvement in vascular health when switching from TC to EC.</p> <p>Ref: Farsalinos KE, Polosa R. Endothelial progenitor cell release is usually considered a beneficial effect: Problems in interpreting the acute effects of e-cigarette use. <i>Atherosclerosis.</i> 2017 Mar;258:162-163. doi: 10.1016/j.atherosclerosis.2016.12.016. George J et al. (2019) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes <i>Journal of the American College of Cardiology</i>:26855 doi:10.1016/j.jacc.2019.09.067</p>	See Table 1, answer 1.
224	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 49, lines 1-20 With regards to the switching to e-cigarettes from conventional cigarettes there is evidence available to suggest that EC’s do not change lung function and specifically reduce the number of flare-ups of COPD Polosa et al 2018</p> <p>Ref: Polosa et al (2017). Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. https://doi.org/10.2147/COPD.S161138</p>	See Table 1, answer 1.

225	Saunders Emily, Broughton Nicotine Services, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Pages 51-52 Please be aware that Shearston et al (2019) is a protocol for a study that has not yet reported any findings. The one paper discussed that evaluates passive exposure, (Ballbe et al, 2014) found that ‘The airborne markers were statistically higher in conventional cigarette homes than in e-cigarettes homes (5.7 times higher).’ This is also cited in the report by PHE (2018) which states ‘In summary, to date there have been no identified health risks of passive vaping to bystanders.’ PHE also comments on the fact that while airborne nicotine levels may rise during EC use, this does not lead to concerning rises in blood nicotine levels in bystanders.</p> <p>Ref: Ballbè et al (2014). Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. Environ Res. 2014 Nov;135:76-80. doi: 10.1016/j.envres.2014.09.005.</p>	The paper by Shearston et al. has been deleted in the final Opinion..																		
226	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Pages 46-47</p> <p>The SCHEER opinion wrongly compares electronic cigarettes with regard to the risks of their use with non-smoking. This does not reflect the fact, that the electronic cigarettes are mostly used as alternatives to smoking. There is strong evidence showing that electronic cigarettes are less harmful than cigarettes.</p> <ul style="list-style-type: none"> • Polosa R et al. Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. International Journal of COPD 2018;13 2533–2542 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113943/ • McNeill A, Brose LS, Calder R, Bauld L & Robson D (2018). Evidence review of ecigarettes and heated tobacco products 2018. A report commissioned by Public Health England. London: Public Health England. https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review/evidence-review-of-e-cigarettes-and-heated-tobacco-products-2018-executive-summary. <p>Ref: Miler (2016). Changes in the Frequency of Airway Infections in Smokers Who Switched To Vaping: Results of an Online Survey. Article in Journal of Addiction Research & Therapy January 2016 DOI: 10.4172/2155-6105.1000290</p>	See Table 1, answer 1.																		
227	Ciprian Boboi, Asociatia Industriei	6.5.4 Human evidence for health impacts of	<table border="0"> <tr> <td>P</td> <td>47/</td> <td>L</td> <td>18</td> <td>-</td> <td>25</td> </tr> <tr> <td>P</td> <td></td> <td>47/</td> <td></td> <td>L</td> <td>29</td> </tr> <tr> <td>P</td> <td>48/</td> <td>L</td> <td>10</td> <td>-</td> <td>47</td> </tr> </table>	P	47/	L	18	-	25	P		47/		L	29	P	48/	L	10	-	47	Identical with comment 230, see the response to that comment.
P	47/	L	18	-	25																	
P		47/		L	29																	
P	48/	L	10	-	47																	

	de Vaping (Vaping Industry Association),Romania	electronic cigarettes	P	51/	L	27	-	55		
										
				Human_evidence_for_health_impacts_of_el						
228	Human Delon,Physician,United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes							By far the most troubling assessment in this Preliminary - that “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong”. Firstly, recognised evidence-based medicine databases, such as the Cochrane Collaboration, does not share this view. Secondly, no robust risk assessment analysis was performed on those e-cigarette users, who were former cigarette smokers. This to determine the the expected health benefits from quitting or switching. More importantly, this section seems to suggest that the acute effects of e-cigarettes on the cardiovascular system, have been used to predict long term effects, with little or no comparators such as caffeine, exercise or medicinal nicotine replacement therapy (1,2) . Is there therefore strong evidence that exercise, likewise has strong negative effect on the cardiovascular system.	The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.
									1. Adamopoulos D, et al. Acute effects of nicotine on arterial stiffness and wave reflection in healthy young non-smokers. Clin Exp Pharmacol Physiol. 2009 Aug;36(8):784-9. 2. Lefferts WK, et al. Effects of acute aerobic exercise on arterial stiffness and cerebrovascular pulsatility in adults with and without hypertension. J Hypertens. 2018 Aug;36(8):1743-1752.	
229	Juusela Maria, Doctors against tobacco (DAT) Finland,Finland	6.5.4 Human evidence for health impacts of electronic cigarettes							There is nothing about fetal safety in the SHEER preliminary opinion. According to animal studies nicotine is strongly toxic to fetus, especially to the development of brain, lungs and autonomic nervous system (Holbrook et al. 2016, England et al 2017). Nicotine is an indisputable neuroteratogen, exposure to which during gestation disturbs all phases of brain development. Electronic cigarettes seem to harm brain development similarly (Sailer et al. 2019). The effects of nicotine on lung development during pregnancy are apparent in many ways: aberrations at molecular level, permanent structural changes, functional disturbances and as increase in pulmonary diseases. In addition, responses of autonomic nervous system linked to hypoxia weaken and mortality increases. Epigenetic changes, shown also to be	There are a lack of data on this point.

caused by nicotine (England et al. 2017), and which unfortunately can be inherited trans-generationally, are regarded as one likely mechanism for developmental origin of disease (Knopik et al. 2012).

Exposure to vaping-induced chemicals depends on the device and the voltage used. Regardless of the primary vaping product the aerosols include harmful chemicals that are carried to surroundings in small liquid droplets. Particulate matter at vaping conventions are comparable with levels found in bars and nightclubs where smoking is allowed. (Melström et al. 2017; Walley et al. 2019). Passive exposure to particles and nicotine from nicotine containing electronic cigarettes resembles closely passive exposure from regular cigarettes (Walley et al. 2019). In addition, toxic compounds, e.g. nicotine, are deposited on clothes and surfaces from which bystanders including children can be exposed (Almeida-da-Silva et al 2020). The health effects of the secondary and tertiary passive exposure to electronic cigarettes have been identified as risk factors for inflammatory and cardiovascular diseases in animal models (Eaton et al. 2018; Marcham & Springston 2019; Walley et al. 2019). They are likely in humans, too (StClaire et al. 2020).



ref-229.docx

There is no specific mentioning of harm reduction in the specific ToR (Section 2.1). The mentioning of harm reduction in the background is linked to cessation (“their role in harm reduction/cessation of traditional tobacco smoking” – so their role for reducing harm through cessation. There is no stand-alone harm reduction point in these ToR. Therefore the SCHEER Opinion focuses only on health impacts compared to non-smoking.

The Opinion was updated highlighting this position in Abstract, Summary, the Scientific Opinion (Section 3) and the Introduction of the Rationale (Section 6.1).

230	Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.5.4 Human evidence for health impacts of electronic cigarettes	P 47/ L 18 - 25 The Committee cites Palamidas as reporting increases in Heart Rate (HR) after acute 1-hour ad libitum use of an unknown ENDS device containing 11 mg nicotine. Contrary to these results, Cossio et al performed a study of 16 healthy smoking naive participants and reported that there was no significant increase in heart rate (HR) or blood pressure (BP) after acute use of either a 0% or 5.4% nicotine ENDS product. In other studies that have reported increased in HR after acute usage, it was noted that these increases were smaller in comparison to those induced by the use of combustible cigarettes (Franzen et al 2018; Szołtysek-Bołdys et al 2014; Yan and D’Ruiz 2015). One study found that ENDS users had to use the product for 6x
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The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.

longer to approach the increases in HR and BP observed after smoking one conventional cigarette (Vlachopoulos et al 2016). These acute changes in BP and HR have been shown to be attributed solely to nicotine (Antoniewicz et al 2019; Chaumont et al 2018).

P 47/ L 29
The statement that "the most consistent evidence regarding the effect of electronic cigarettes on human health concerns cardiovascular diseases" is based on the European Heart Network's opinion. However, large clinical studies show that the moderate acute effects of nicotine on heart rate and blood pressure are not associated with increased cardiovascular risk. Mills et al (2014) (*1) found "no clear evidence of harm" when they examined the cardiovascular effect of a variety of nicotine replacement therapies; since the nicotine used in e-cigarettes is of the same grade (as specified in the European Pharmacopeia) there is no reason to suspect that the nicotine contained in e-cigarettes has a different effect. Benowitz et al (2018) (*2) reported findings along similar lines when reviewing the cardiovascular effects of nicotine replacement therapies.

P 48/ L 10 - 47
This section, which reviews the potential cardiovascular risks of nicotine use, focuses on the cardiovascular effects of nicotine. However, the long-term epidemiological data on nicotine use without smoke - for example through the use of licensed nicotine replacement therapies (which have been on the European market for many decades) - do not indicate that such use results in serious health effects. Inline 10, for instance, attention is drawn to Vlachopoulos et al (2016) on the effects of electronic cigarette use on arterial stiffness, which concludes that e-cigarette use can contribute to aortic stiffness. The same authors undertook a similar study on caffeine (*3) which came to similar conclusions on the effects of caffeine on aortic stiffness. However, this does not mean that there is a clear link between nicotine use and cardiovascular diseases due to the routine use of either nicotine or caffeine (see Wilson and Bloom, 2016) (*4).

The Committee fails to acknowledge that the relevant marker for cardiovascular risks is what happens to the cardiovascular system when smokers switch to e-cigarettes. George et al (2019) (*5) examined this in their paper “Cardiovascular effects of switching from tobacco cigarettes to electronic cigarettes”. The conclusion is clear: that smokers (and in particular female smokers) “demonstrate significant improvement in vascular health within 1 month of switching from TC to EC”.

P 51/ L 27 - 55

The studies that are cited in this section of the Committee’s report are completely unrelated to electronic cigarettes. In fact, they relate only to the exposure that is foreseeable from combustible cigarettes, meaning that the data is of no value in this context. Surprisingly, the Committee has chosen to use data related to the exposure to cigarette smoke in its conclusion about emissions from electronic cigarettes.

Ref:

* 1 -<https://pubmed.ncbi.nlm.nih.gov/24323793/>

* 2- <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2677060>

* 3- https://journals.lww.com/jhypertension/Abstract/2003/03000/Effect_of_caffeine_on_aortic_elastic_properties.22.aspx

* 4- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4859405/>

* 5- <https://pubmed.ncbi.nlm.nih.gov/31740017/>

231	Arnett Deborah, Action on Smoking and Health UK, United Kingdom	6.5.4 Human evidence for health impacts of electronic cigarettes	<p>Page 47-48</p> <p>SCHEER concludes that the evidence of long-term systemic effects on the cardiovascular system is strong, yet the Opinion does not include evidence to support this conclusion. In fact the evidence is weak and insufficient largely resting on the erroneous assumptions that the short-term cardio-vascular impact of nicotine necessarily translates to long-term harm. This is not the conclusion reached by the UK’s Medicines and Healthcare products Regulatory Agency (MHRA) when in 2010 NRT was licensed for long-term use, without any restrictions on duration. To the contrary the MHRA concluded that “Although nicotine per se has potent pharmacological effects (including increased heart rate and constriction of blood vessels), there is a large body of evidence that medicinal nicotine (in currently licensed forms) is not a significant risk factor for cardiovascular events, and does not cause cancer or respiratory disease.”</p>
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The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.

			<p>With respect specifically to e-cigarettes, there are now a number of longer-term human clinical trials that find that switching from tobacco cigarettes to e-cigarettes has a beneficial impact on the cardiovascular system which do not appear to have been included in the review. See: D’Ruiz et al 2017 https://pubmed.ncbi.nlm.nih.gov/28476553/ Farsalinos et al 2017 https://pubmed.ncbi.nlm.nih.gov/26749533/ George et al 2019 https://www.onlinejacc.org/content/74/25/3112</p>	
232	<p>Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Sweden</p>	<p>6.5.4 Human evidence for health impacts of electronic cigarettes</p>	<p>At page 48, lines 12 - 16, SCHEER cites two studies regarding CVD onset and progression: “Furthermore, electronic cigarette use is also associated with key underlying pathophysiological mechanisms implicated in CVD onset and progression, including endothelial cell dysfunction and oxidative stress (Higashi et al., 2009, Moheimani et al., 15 2017) similar to that of tobacco smoking, including rapid surges in the number of circulating endothelial progenitor cells (Antoniewicz et al., 2016), ultimately inducing vascular injury.” The studies reference above relate to the harmful effects of e-cigarettes on vascular endothelial functions although we note that the paper quoted by Higashi et al., 2009 (doi:10.1253/circj.cj-08-1102DOES) does NOT relate to the use of e-cigarettes. The paper by Moheimani et al., 15 2017, indicates that caffeine was prohibited from use for a period of 12hrs prior to tests being recorded. This is understandable because caffeine increases oxidative stress levels, but there is no evidence that it carries any long term effects on health. The Moheimani et al. paper concluded that “Although we did not uncover evidence of oxidative stress following acute e-cigarette exposure, further studies are necessary to exclude this possibility.” It also states “further studies investigating additional cardiac risk markers, such as endothelial function using brachial artery flow-mediated dilatation and additional markers of oxidative stress”. In view of the inconclusive results of the research above we wish to bring to your attention a study commissioned by the British Heart Foundation, carried out by the University of Dundee published in November 2019 which concentrates exclusively on the direct impact to human endothelial functions.</p> <p>Jacob George et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. Journal of the American College of Cardiology (JACC) 15-10- 2019.</p>	<p>The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.</p> <p>The Moheimani- study has been excluded from the Opinion.</p> <p>See Table 1, answer 1.</p>

<https://doi.org/10.1016/j.jacc.2019.09.067>

“The purpose of the study was to assess the effects of electronic cigarettes-nicotine and electronic cigarette-nicotine free on endothelial function as compared to traditional cigarettes.”
At the time of publication, this study represented the largest study to date comparing the effect of vaping to smoking on vascular disease

Results

“Within 1 month of switching from TC to EC, there was a significant improvement in endothelial function (linear trend β = 0.73%; 95% confidence interval [CI]: 0.41 to 1.05; $p < 0.0001$; TC vs. EC combined: 1.49%; 95% CI: 0.93 to 2.04; $p < 0.0001$) and vascular stiffness (−0.529 m/s; 95% CI: −0.946 to −0.112; $p = 0.014$). Females benefited from switching more than males did in every between-group comparison. Those who complied best with EC switch demonstrated the largest improvement. There was no difference in vascular effects between EC with and without nicotine within the study timeframe.”

Conclusion

3.5

“...this study supports the conclusion that smokers who switch to vaping will reduce their risk of future heart attacks and other cardiovascular disease. The risk reduces rapidly and is greater in women. However, vaping does carry some risks and is not recommended for non-smokers or young people.”
“Within the EU, e-cigarettes are used predominantly by smokers and former smokers.” (Kaplan et al Section 8 Page 82 P11) and we consider the study by George et al to be of important significance to the SCHEER committee within the context of evaluating cardiovascular risk to e-cigarette users regarding harm effects on human endothelial cells.

Ref: Kapan et al (2020). Use of Electronic Cigarettes in European Populations: A Narrative Review. *Int. J. Environ. Res. Public Health* 2020, 17, 1971; doi:10.3390/ijerph17061971

233 No agreement to disclose personal data 6.5.5 Risk assessment

It is serious that the SCHEER Opinion omits to include a specific section on risk reduction versus conventional smoking both in the abstract and in the Risk assessment chapter. Without that any assessment on electronic smoke is done outside the principle of

See Table 1, Answer 1.

			appropriateness. Such a comparison must be included in the final opinion of the SCHEER.		
234	No agreement to disclose personal data	6.5.5 Risk assessment	pag. 55, line 17-25 It is serious that the SCHEER Opinion omits to include a specific section on risk reduction versus conventional smoking both in the abstract and in the Risk assessment chapter. Without that any assessment on electronic smoke is done outside the principle of appropriateness. Such a comparison must be included in the final opinion of the SCHEER.		Duplication of the previous comment See Table 1, Answer 1.
235	Mayer Bernhard-Michael, University of Graz, Pharmacology and Toxicology, Austria	6.5.5 Risk assessment	page 60, lines 13-16 This statement reflects the WHO's untenable stance, which dismisses studies not fitting to their ideology-driven policy as fraudulent, ad hominem attacks replace scientific discussions. Several studies published by industry-independent groups confirm the findings published by "tobacco employees" or funded by the National Vapers Club (see, for instance [1-3]). The SCHEER implicitly accuses scientists with a high international reputation of publishing fraudulent data. The malicious imputation of severe scientific misconduct without even a hint of evidence is unacceptable and should suffice to exclude all committee members from future activities in public health.		The SCHEER recorded what is found in the review: "It is noted that those studies undertaken by tobacco employees or funded by the National Vapers Club concluded no apparent risk from ECs to bystanders. Those who did not declare a conflict of interest were more likely to draw conclusions that were more precautionary and/or suggested a potential risk from passive exposure to ECs, highlighting potential biases in the current literature." The Opinion has been updated and the WHO (2020) has been added.
			Page 61. lines 1-13 The SCHEER estimated the respiratory risk of users based on the identification of irritants in the aerosols of e-cigarettes without considering that the levels of these substances are far below accepted thresholds for inhalation. Contrary to the SCHEER's claim, clinical studies show that vaping doesn't affect the respiratory function of never-smokers using e-cigarettes for 3.5 years [4] and significantly ameliorates lung function of asthmatic smokers observed for two years [5]. A recent follow-up of an earlier study showed that the objective and subjective outcomes of COPD smokers persist for at least five years after switching to e-cigarettes [6]. Taken together, all clinical studies currently available demonstrate that vaping doesn't cause appreciable impairment of lung function [7].		With regard to the use of "accepted thresholds" in the risk assessment for e-cigarette users the SCHEER has many doubts: see Section 6.5.5.2. The lines of evidence together point at a risk for adverse effects to the respiratory tract. With regard to comparative assessment: See Table 1, Answer 1.
			page 61, lines 15 - 24 The effects of nicotine on the cardiovascular system are well		

established and not a peculiarity of nicotine-containing e-cigarettes. The SCHEER should have considered that smokers switching to e-cigarettes have consumed nicotine before, rendering potential nicotine effects extraneous for over 95 % of e-cigarette users. Extensive epidemiological studies show that nicotine replacement therapy (NRT) doesn't increase cardiovascular risk [8,9]. Since the administration route is irrelevant for systemic effects, the results are equally valid for vaping [10,11]. NRT is recommended to aid cessation of smokers, in Austria, even teenagers above 12 years of age, without warnings from cardiovascular risk. The SCHEER and several other public health bodies, including the WHO, appear to assert nicotine's toxicity only if present in non-medicinal products. A recently published clinical study showed a reversal of smokers' endothelial dysfunction to the level of non-smokers one month after switching to e-cigarettes [12]. Similarly, significant improvement of smokers' vascular function, including aortic stiffness, was observed four months after switching [13]. The SCHEER cherry-picked papers confirming the committee's preconceived opinion. Due to the upload limit, only #4, #6 and #19 (review) are attached. For papers on second-harm exposure and cardiovascular risk, see my replies to sections 6.5.2 and 6.5.4, respectively.

1. McAuley et al. *Inhal. Toxicol.* 24, 850-857 (2012)
2. van Drooge et al. *Environ. Sci. Pollut. Res.* 26, 4654-4666 (2019)
3. Schober et al. *Int. J. Hyg. Environ. Health* 222, 486-493 (2019)
4. Polosa et al. *Sci. Rep.* 7(2017)
5. Polosa et al. *Discov. Med.* 21, 99-108 (2016)
6. Polosa et al. *Ther. Adv. Chronic Dis.* 11(2020)
7. Polosa et al. *Expert Rev. Respir. Med.* 13, 899-915 (2019)
8. Mills et al. *Circulation* 129, 28-41 (2014)
9. Benowitz et al. *JAMA Intern. Med.* 178, 622-631 (2018)
10. Farsalinos et al. *Intern. Emerg. Med.* 11, 85-94 (2016)
11. Farsalinos et al. *Ther. Adv. Chronic Dis.* 10, 2040622319877741 (2019)
12. George et al. *J. Am. Coll. Cardiol.* 74, 3112-3120 (2019)
13. Ikonomidis et al. *Food Chem. Toxicol.* 141, 111389 (2020)

SCHEER took into account the suggested literature and rephrased the Opinion in some parts, accordingly.

236 Landl Michael, World Vapers' Alliance, Austria
6.5.5 Risk assessment

Pages 60 - 62: Regarding your concluding remarks, we absolutely agree and do not contest the fact that e-cigarettes are not risk free. However, we see as a main missing feature of this preliminary opinion a comparison in terms of the level of harm exhibited by e-cigarettes as opposed to traditional cigarettes. There is strong evidence from a number of studies that e-cigarettes are less harmful by a large degree than traditional cigarettes. [1] [2] [3]
References:

See Table 1, answer 1.

[1][2] Ann McNeill, Leonie Brose., Robert Calder., Linda Bauld Debbie Robson, Vaping in England: an evidence update including mental health and pregnancy, March 2020;

[2] Fédération des professionnels des addictions, POSITION DE LA FÉDÉRATION DES PROFESSIONNELS DES ADDICTIONS SUR LE VAPOTAGE

237 Martinez Javier, JT International SA, Switzerland

6.5.5 Risk assessment

P.60. 1.9 Hess 2016 study referenced did not identified actual health risks because the study did not report on the level of exposure of e-cigarette aerosol. Public Health England concluded, “In summary, to date there have been no identified health risks of passive vaping to bystanders.” (McNeill, 2018). A study authored by researchers affiliated to the RIVM, Visser et al 2019, cited by SCHEER concluded, “To the best of our knowledge, this represents the first toxicological risk assessment of e-cigarette vapor to bystanders. While health effects to bystanders are expected, the effects are relatively mild, even in extreme scenarios.” Please refer to a study that assessed the physical properties of exhaled e-cigarette aerosol constituents at different distances from an artificial bystander. (Martuzevicius et al. 2019) According to the authors, the results of this study provide reinforcing evidence that vaping has minimal impact on indoor air quality. A study examined air in an experimental chamber with an air exchange rate typical for office buildings where a dozen of e-cigarette users used different e-cigarette devices for four hours. (Liu et al. 2017) The authors conclude, “Overall, our results indicate that under the study conditions with the products tested, cumulative room air levels of the selected chemicals measured over 4-h were relatively small and were several-fold below the current occupational regulatory and consensus limits.”

P.60, 1.44-45 SCHEER states that “long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking.” Please provide complete scientific evidence supporting that “long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer” or revise or remove this statement. We are not aware of any human study demonstrating that “long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer.” in adult smokers switching to e-cigarettes. Current

The SCHEER conclusion on second-hand exposure risks is based on several lines of evidence: overall, the weight of evidence for these risks is considered low to moderate, the strongest evidence being for irritative effects on the respiratory tract. So we are a bit more cautious that the PHE-report, mainly based on the results of the Visser studies.

The SCHEER has updated this section with the literature suggested (Martuzevicius, Liu).

evidence does not support the idea that nicotine is a human carcinogen, let alone a complete carcinogen. (see Surgeon General, 2014, stating, “There is insufficient data to conclude that nicotine causes or contributes to cancer in humans”. An accurate assessment of the health effects of e-cigarettes is dependent on the context of age, current and prior use of combustible tobacco products, and whether the user has preexisting conditions, such as asthma and COPD. Please be more specific when referring to “some other diseases also associated with smoking” and provide complete scientific evidence supporting that “long-term use is expected to increase the risk of [...] some other diseases also associated with smoking.”

P.61, 1.15 onwards The statement, “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” is inconsistent with the scientific literature. We note that SCHEER omitted a significant amount of the scientific literature regarding the cardiovascular effects of e-cigarettes. To date, the evidence for effects of e-cigarettes on long-term cardiovascular health in individual e-cigarette users is inconclusive. Please refer to our extensive comment and additional scientific studies provided under section 6.5.4 p.47, 1.27 onwards and under section scientific opinion P.15, 1.1-14. Please amend this statement to reflect a more comprehensive review of the literature highlighting the insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function in smokers who had switched to e-cigarettes.

238 Champagnac Maxime, Phoebe, France

6.5.5 Risk assessment

p56 lines 53-56 "Visser et al. (2014 and 2015a) performed a risk assessment based upon three pre-defined exposure scenarios for daily users. They used the 54 aerosol analysis data for two out of the 12-17 e-liquid samples shown in Section 6.5.2, table 3 and the calculations explained in the previous section. " Not relevant of the market as they found nitroamines when it is said in visser et al 2015" A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." This risk assessment was realized with products before the TPD implementation, and Not relevant of the market as they found nitroamines when it is said in visser et al 2015" A small proportion

See Table 1, answer 4.

of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." This assessment suits only for product with Tobacco extracts leadings to TNSA

239	Champagnac Maxime,Phode,France	6.5.5 Risk assessment	p58 line 22 from the second hand exposure TSNA should not be there "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."	See Table 1, answer 4.
240	Champagnac Maxime,Phode,France	6.5.5 Risk assessment	p62 line 36 -37 "The overall weight of evidence for a carcinogenic risk due to cumulative exposure to TSNAs is weak to moderate. " TNSA are unlikely to be found in a majority of liquid as they come from tobacco extracts. Tobacco extract leading to TNSA should be regulated	See Table 1, answer 4. Indeed, the presence of TNSA is related to presence of impurities in the nicotine batches used in the formulations of the e-liquids; as the purity of nicotine is not sufficiently regulated, the presence of TNSA cannot be excluded.
241	Champagnac Maxime,Phode,France	6.5.5 Risk assessment	p58 Second hand exposure. In Visser 2016 there is chronic overestimation of the second hand exposure using the 50% of the nicotine exhaled (like in smoke) when it is shown that is only 5% https://www.rivm.nl/bibliotheek/rapporten/2016-0036.pdf The scenario with 50% nicotine exhaled like in smoke isn't applicable to the vapor as 95% of the nicotine is absorbed. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/	See Table 1 answer 4.
242	Vejdovsky Katharina, AGES – Austrian Agency for Health and Food Safety, Austria	6.5.5 Risk assessment	6.5.5.3 Risk Assessment Page 57, lines 22-23: The description of the conducted risk assessment is not transparent. The ultimately important information is not given. A detailed list of applied points of departure for each substance and according elucidations, which MOE would be sufficient to reach a conclusion of low concern (as it is described on page 56, lines 33-46) is not given. This information is needed to form an objective independent expert's opinion on the methodological soundness of the applied procedure. In addition, the lack of this information prevents the reproduction of the risk assessment.	Thank you for this comment. All values of the MoEs are reported by SCHEER as well as the conclusions from the authors based on these MoEs. PoDs can easily be recovered from the literature cited.

It is not clear whether the risk assessment results are calculated separately for this opinion, or whether they are taken from the previous study (Visser et al. 2014). This original study might include the lacking information regarding PoDs and MOEs, yet it is not available in English. An English translation (Visser et al.

2015) of this study represents only a short version and does not include PoDs and MOE assessments. Visser, W., Geraets, L., Klerx, W., Hernandez, L., Stephens, E., Croes, E., Schwillens, P., 6 Cremers, H., Bos, P., Talhout, R. (2014). De gezondheidsrisico's van het gebruik van e-7 sigaretten. National Institute for Public Health and the Environment, Bilthoven, the 8 Netherlands, RIVM report 2014-0143 (in Dutch), Available from: 9 <http://www.rivm.nl/bibliotheek/rapporten/2014-0143.pdf> 10 11 Visser, W., Geraets, L., Klerx, W., Hernandez, L., Stephens, E., Croes, E., Schwillens, P., 12 Cremers, H., Bos, P., Talhout, R. (2015). The health risks of using e-cigarettes. National 13 Institute for Public Health and the Environment, Bilthoven, the Netherlands, RIVM rapport 14 2015-0144, Available from: <http://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf>

243 No agreement to disclose personal data 6.5.5 Risk assessment

Page 61 L30: SCIENTIFIC LITERATURE SHOWS AEROSOLS FROM E-CIGARETTES WHICH ARE MANUFACTURED TO ROBUST QUALITY AND SAFETY STANDARDS CONTAIN SUBSTANTIALLY LOWER LEVELS OF TOBACCO-SPECIFIC NITROSAMINES (TSNAs) COMPARED TO CIGARETTE SMOKE

The concentrations of the tobacco-specific nitrosamines (TSNAs) e-cigarettes have been shown to be orders of magnitude lower than in tobacco smoke [e.g. 1]. Through the use of pharmaceutical grade quality nicotine in e-cigarettes, levels of any TSNAs contaminants are extremely low and within the acceptable tolerances for medicinal nicotine products. The US National Academics of Sciences, Engineering and Medicine report[2] note “Low levels of TSNAs have been reported in e-cigarette liquids and aerosol, typically at levels similar to those found in pharmaceutical nicotine products. This is probably attributed to the use of pharmaceutical grade nicotine that most manufacturers claim to use. This grade of nicotine is highly purified to remove the majority of impurities, including TSNAs.” Similarly, the UK Government’s Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) recent and comprehensive report also reported “The Committee considered that available data indicated that exposure to TSNAs from [e-cigarette] aerosols is likely to be very low” (page 22)[3]. Studies have shown that e-cigarette aerosols contain low or no detectable levels of TSNAs (e.g. >99% reduction compared to cigarette smoke[4]) which directly translates into rapid and substantial reductions in exposure to TSNAs in adult smokers’ bodies when they transition to e-cigarettes[5] & [6]. Specifically, e-cigarette users have been shown to experience a 97% reduction in

See Table 1, answers 1 and 4.

See Table 1, Answers 1 and 4. The SCHEER considers the overall evidence for the carcinogenic risk low to moderate and points at a role for cumulative exposure. Scungio et al. (2018) which was described in Section 6.5.5.4 indeed shows low calculated risk estimates. It is noted that study is based on a continuous exposure scenario. Nevertheless, this line of evidence indeed could have been included in the conclusion in Section 6.5.5.6. This is corrected in the final Opinion.

exposure to NNAL (a marker for TSNAs) with concentrations 2 ng/g creatinine in non-users, 6 ng/g in e-cigarette users and 285 in smokers[7].

P61 L15: BASED ON THE TOTALITY OF THE AVAILABLE SCIENTIFIC EVIDENCE, IT IS INCORRECT TO CONCLUDE “THE OVERALL WEIGHT OF EVIDENCE FOR RISK OF LONG-TERM SYSTEMIC EFFECTS ON THE CARDIOVASCULAR SYSTEM IS STRONG” (see our response for section 6.5.4, in reference to SCHEER’s opinion page 54, line 52).

P61 L29: AN OPTIMAL COMBINATION OF VAPE DEVICE SETTINGS, LIQUID FORMULATION AND E-CIGARETTE USE RESULT IN EMISSIONS WITH MUCH LESS CARCINOGENIC POTENCY THAN TOBACCO SMOKE E-cigarette aerosols have been shown to have a cancer risk potency <1% compared to tobacco smoke[8]. Although SCHEER cite this study in their opinion, they fail to report the estimated cancer risk of e-cigarette aerosols compared to tobacco smoke. Moreover, the corresponding Excess Lifetime Cancer Risk value of mainstream e-cigarette aerosols has been estimated to be $6.11-7.26 \times 10^{-6}$, which is 5 orders of magnitude lower than that of mainstream combustible cigarette smoke, and also lower than the guideline values defined by EPA and WHO [9].



6.5.5_Risk_assessment.pdf

CVD hazard under chronic conditions is already addressed above in other comments.

244 Chaplia Maria,Con sumer Choice Center,United States

6.5.5 Risk assessment

PAGES 60 - 62: We absolutely agree that e-cigarettes are not risk-free. However, we see as a main missing feature of this preliminary opinion a comparison in terms of the level of harm exhibited by e-cigarettes as opposed to traditional cigarettes. There is strong evidence from a number of studies that e-cigarettes are less harmful by a large degree than traditional cigarettes.
McNeill (2020) Vaping in England: an evidence update including mental health and pregnancy, March 2020
Fédération des professionnels des addictions (2017) POSITION DE LA FÉDÉRATION DES PROFESSIONNELS DES ADDICTIONS SUR LE VAPOTAGE

See Table 1, answer 1.

245	Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.5.5 Risk assessment	<p>https://www.grea.ch/sites/default/files/171019_positionspapier_vapotage_0.pdf</p> <p>P. 56-58, to all of Section 6.5.5.3 We believe that taking only results from the Dutch studies may lead to wrong results for e-cigarette users in other European countries. In this chapter the publications of other RIVM authors, Visser et al. (2014, 2015, 2016, 2019) are discussed. Although Table 3 shows a range of aerosol constituents of several Dutch e-liquids, the risk assessment was based on two Dutch e-liquids from the first generation of e-liquid cartridges (no. 6 and no. 172) with high nicotine contents (19 mg/ml and 16.8 mg/ml). The conclusions in the SCHEER's Opinion for the nicotine exposure of heavy users may not be transferable to consumers of the other Member States taking into consideration results from Belgian e-cigarette users. Smets et al. (2019) found that nicotine concentration in e-liquids used vary greatly from country to country, e.g. Belgian vapers used e-liquids with a significantly lower nicotine concentration but consumed much more of it. Depending on subcultural and/or geographic parameters, heavy users may have the tendency to use low concentration e-liquids.</p> <p>P. 57 l. 49-52 We believe that the statement on p. 57 l. 49-52 is not generally applicable. The amount of carbonyls produced is very much dependent of the type of e-cigarette used. Some e-cigarettes produce more formaldehyde per puff as a conventional cigarette whereas many others have formaldehyde concentrations that are 99% reduced compared to conventional cigarette smoke.</p> <p>P. 58 l. 13 “Assessment of second-hand exposure”: The aerosol concentration in different regions of the respiratory tract cannot be measured. Therefore, simulations are necessary for risk assessments. However, various second-hand exposure scenarios can be experimentally setup and aerosol concentrations can be measured. For the second-hand exposure risk assessment, we believe the measured aerosol concentrations should be preferred.</p> <p>P. 60 l. 13-15 We suggest to remove the statement “but these studies were</p>	<p>The SCHEER concluded (6.4) that information indicates that the content of ingredients in e-liquids shown for the Netherlands and in Greece are representative for the EU market in general. Therefore the results of the Visser studies are believed to be extrapolatable to other EU countries.</p> <p>The SCHEER agrees that the carbonyl emissions are highly variable and this conclusion is in Section 6.5.2.3. Because of the extremely variable individual differences in the levels of exposure, to ingredients in liquids and aerosol the SCHEER based her risk assessment on the controlled studies of Visser <i>et al.</i></p> <p>The SCHEER agrees and based her risk assessment on measured data in controlled studies.</p> <p>The SCHEER recorded what is observed in the review: "It is noted that those studies undertaken by tobacco employees or funded by the National Vapers Club concluded no apparent risk from ECs to bystanders. Those who did not declare a conflict of interest were more likely to draw conclusions that were more precautionary and/or suggested a potential risk from passive exposure to ECs, highlighting potential biases in the current literature."</p>
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reported to have been undertaken by tobacco employees or funded by the National Vapers Club”. Studies published in reputable peer reviewed journals should not be dismissed or negatively judged. An appropriate and accepted way to scientifically evaluate publications is the Klimisch scoring (Klimisch et al., 1997).

Paragraph 6.5.5.5

We suggest to use the updated Cochrane systematic review of epidemiological studies for e-cigarettes (Hartmann-Boyce 2020; update of Hartmann-Boyce 2016, and McRobbie 2014) with the conclusion that “[C]onfidence intervals were wide for data on AEs [adverse events], SAEs [serious adverse events] and other safety markers. Overall incidence of SAEs was low across all study arms. We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.”

Ref.:
 Hartmann-Boyce 2016 Cochrane Database of Systematic Reviews
 Hartmann-Boyce 2020 Cochrane Database of Systematic Reviews
 Klimisch 1997 A Systematic Approach for Evaluating the Quality of Experimental
 McRobbie 2014 Cochrane Database of Systematic Reviews
 Smets 2019 When Less is More Vaping Low-Nicotine vs high Nicotine e-liquids

Thank you. The section was updated with this systematic review.

246 Stucki
 Andreas,P
 ETA
 International Science Consortium Ltd.,Germany

6.5.5 Risk assessment

Thank you to SCHEER for providing a comprehensive opinion on electronic cigarettes.

Page 56, lines 34+35:

It states that “A MoE is the ratio of a reference point (the Point of Departure or PoD), often taken from an animal experiment and corresponding to an exposure that causes a low but measurable response...”

The SCHEER agrees. The definition was adjusted as indicated.

Suggestion: Please edit the sentence as below:
 “A MoE is the ratio of a reference point (the Point of Departure or PoD), taken from in vitro or in vivo experiments and corresponding to an exposure that causes a low but measurable response...”

We would like to point out that a PoD can also be derived from in vitro experiments. The current sentence could be interpreted as an endorsement for animal testing as it seems that animal experiments are necessary for risk assessment. In the Opinion on Additives used

Current assessment is based on existing studies, which are animal studies and human studies. In general, the SCHEER supports to avoid performing new animal studies. The SCHEER has made a statement on this in the Opinion.

in tobacco products (Opinion 2) from 2016 (https://ec.europa.eu/health/sites/health/files/scientific_committee/scheer/docs/scheer_o_001.pdf), the SCHEER wrote on page 5: “For ethical reasons, the performance of new animal studies is not endorsed to assess the contribution of an additive to the tobacco product toxicity. Therefore, as a principle, only in silico and in vitro studies should be considered for new testing in Step 3, following the EU policy to ban animal studies for chemicals to be used in voluntary products.” (Abstract, page 5). These sentences are also true for electronic cigarettes and animal methods should not be endorsed.

We would welcome if the SCHEER considered adding a statement discouraging the use of animals to its opinion on electronic cigarettes. The below paragraph, adapted from the tobacco additives opinion, is a suggestion for such a paragraph:

For ethical reasons, the performance of new animal studies is not endorsed to assess the risk of electronic cigarettes. Therefore, as a principle, only in silico and in vitro studies should be considered for new testing, following the EU policy recommending implementation of 3R methods for refinement, reduction, and replacement of animal models, leading to the ban of animal studies for chemicals to be used in voluntary products such as cosmetics (EU Regulation no. 1223/2009). Non testing or alternative testing approaches followed for the evaluation of cosmetic ingredients, whenever relevant to electronic cigarettes, could be considered.

247 Arffman Päivi, Vapers
Finland, Finland

6.5.5 Risk assessment

Assessment for second-hand exposure: “Scungio et al. (2018) evaluated the excess lifetime carcinogenic risk (ELCR) of [...] second-hand smoke from electronic cigarettes and found about two orders of magnitude of difference between ELCR associated to mainstream aerosol (that were below 1.10^{-5}) and second-hand aerosol.” (Page 60, lines 16-19). In the same study it is also mentioned that: “The corresponding ELCR value of mainstream EC [electronic cigarette] aerosol [...] is 5 orders of magnitude lower than that of mainstream traditional cigarettes smoke, and also lower than the guideline values defined by EPA and WHO. Particle number concentrations [...] were measured in second-hand aerosol

Scungio et al. (2018) was described in Section 6.5.5.4 indeed shows low calculated risk estimates. It is noted that study is based on a continuous exposure scenario. Nevertheless, this line of evidence indeed could have been included in the conclusion in Section 6.5.5.6. This is corrected in the final Opinion.

vapourised nicotine products including e-cigarettes with those of tobacco smoke”. The central finding of this study is that e-cigarette users are typically exposed to 0.4% of the lifetime cancer risk of smokers, but this finding does not seem to have been considered in the SCHEER report despite the committee having read the study. It is clearly relevant to the risk assessment and should be included in the narrative as well as considered in the scientific opinion.

P 60 – 61; L 55 - 13
 The risks of irritative damage to the respiratory tract are not placed in the context of the comparable risks associated with smoking. This leads the SCHEER to characterise a risk that applies to never-smoking users who, according to Eurobarometer data, make up a tiny fraction of total users of e-cigarettes in Europe. A number of studies show that for smokers, there is significant benefit to the respiratory system in those who switch to e-cigarette use. Polosa (2014) undertook an examination of asthmatics who had switched - either completely or partially - to e-cigarette use from smoking. The study concluded: “Overall there were significant improvements in spirometry data, asthma control and AHR...No severe adverse events were noted...this study shows that e-cigs can be a valid option for asthmatic patients who cannot quit smoking by other methods.”



Risk_assessment.pdf

249	Olteanu Vlad, Juul Labs Inc., Belgium	6.5.5 Risk assessment	Page 56, line 33: “As a pragmatic alternative, the Margin of Exposure (MoE) approach may be applied.”The MoE section in the report lacks transparency and does not allow the reader to determine if the MoEs are accurate. The MoE is calculated as the No Observed Adverse Effect Level (NOAEL) divided by the Estimated Human Exposure (EHE). The NOAEL does not take uncertainty into consideration, necessitating the need for MoE to be compared with Uncertainty Factors (UFs). Where and which UFs were applied for each MoE were not provided making interpretation and appropriate application difficult. Page 56, lines 40–43, states that, “In general, only interspecies and inter-individual differences in susceptibility need to be taken into account in the evaluation of the MoE if no	The SCHEER refers to the publications cited for the exact quantitative values of the MoEs. The Visser studies are the only experimental studies available with controlled conditions and realistic use topography, whereas the risks are estimated using the MoE approach. Other risk assessments predominantly compare exposure levels of substances in aerosol from electronic cigarettes with health based guidance values and this approach is considered less suitable since these ignore the toxicokinetics and dynamic of e-cigarette use as explained in Section 6.5.5.2. Therefore the SCHEER does not agree with the comment that “the MoE approach would not be appropriate if Health Based Guidance Values (HBGVs),
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adverse effects are observed at the PoD. Typically, a MOE of minimally a factor of 100 is then considered to be required for non-carcinogenic effects.” Without knowing the UFs for a particular MoE, the MoE cannot be interpreted and risk cannot be assessed. Please note that the MoE approach would not be appropriate if Health Based Guidance Values (HBGVs), such as RfCs, were used instead of NOAELs. Hazard Quotients should be used with HBGVs. Page 56, Lines 3 – 31. 6.5.5.2 Dose metrics in the risk assessment of electronic cigarettes. “In risk assessment, the hazard information preferably needs to show an exposure regimen close to that of the exposure scenario under investigation..[to line 31]” Although toxicity reference values developed for the general and occupational populations are not intended to be used for tobacco product exposure evaluation, they can inform the overall toxicity of tobacco products. As noted by the US FDA in their 2019 memo outlining the Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products, Toxicity reference values for the general population are considered to be the most health protective and therefore preferable for estimating any potential hazards and risks. In contrast, the use of Occupational Exposure Limits may only inform the toxicity evaluation for non-cancer effects. Page 58, Line 54 – 57; Page 59, Lines 1 – 6. “Several reviews are available that predominantly compare exposure levels of substances in aerosol from electronic cigarettes with health-based guidance values..such risk assessment are not applicable for the purpose of this Opinion, unless they show that the puff concentrations measured are below these standards and therefore clearly point at the absence of any risk with a wide margin.” The majority of e-cigarette constituents in aerosol including HPHCs, are at reduced levels or BLOD/BLOQ, indicating substantial lower concentrations in the lungs (peak concentrations) compared to conventional cigarettes. The analytical chemistry data reported by Czekala (2019) show that with the exception of the base e-liquid ingredients, the levels of all measured constituents, including established and proposed HPHCs with known respiratory toxicities are reduced in e-cigarette aerosols compared to smoke from conventional cigarettes. Czekala (2019) reported > 99% reduction in the e-cigarette aerosol of respiratory toxicants including the potent respiratory toxicants acrolein, acrylonitrile and 1,3-

such as RfCs, were used instead of NOAELs”. Of course, such comparisons are valid for second-hand exposure.

With regard to the comparison with smoking: see Table 1, answer 1.

butadiene. Among all respiratory toxicants, only the aerosol level of acrolein (peak concentration) exceed its extremely low reference concentration. The aerosol levels for the remaining constituents with respiratory toxicity were below their respective reference values, suggesting low or no risk for respiratory effects. These data indicate that for the majority of the e-cigarette aerosol constituents, peak concentration of e-cigarette aerosols are below their health-based guidance values. Please respect copyright rules of uploaded studies.

Ref:

Ayala-Fierro (2019). Poster. Quantitative risk assessment (QRA) indicates reduced risk potential for carcinogenic and non-carcinogenic effects of the aerosol of the next generation products (NGPs) compared to reference cigarettes. CORESTA Meeting, Smoke Science/Product Technology, 2019, Hamburg, STPOST 33

ECHA (2013). Guidance For Human Health Risk Assessment Volume Iii, Part B Guidance On Regulation (EU) No 528/2012 Concerning The Making Available On The Market And Use Of Biocidal Products (BpPR) Version 1.0 December 2013

FDA. (2019) Memorandum. Inhalation Reference Values in Toxicological Evaluations.

250 Vuerich Michela, A NEC, European Consumer voice in standardisation, Belgium

6.5.5 Risk assessment

Page 55, lines 29-30: We cannot see why a prioritisation should be (only) based on existing concentration measurements in the aerosol. The concentrations in the aerosol can be calculated easily based on the concentration of substances in the e-liquid when complete aerosolisation can be assumed.

SCHEER disagrees with the view that reporting the level of emissions per liquid consumption rather than puffs is essential and relevant to true exposure. This approach ignores the toxicokinetics and dynamics of exposure via aerosols during use of e-cigarettes as explained in Section 6.5.5.2 and may lead to an underestimation of the risk for which the actual concentration in the puff is the most relevant exposure parameter. Of course, there is high variability in these exposure estimation given the number of conditions that can change as noted in the comment.

Page 55, lines 48-50: The statement that Table 5 is the most comprehensive list and that the substances identified by ANEC are included therein is grossly misleading. It holds true only for the elements (ANEC considers Cd, Ni, Pb relevant). In fact, ANEC has calculated limits for 39 substances in e-liquids (3 metallic contaminants and 36 flavours) and limits for 7 substances in emissions (3 metallic contaminants and 4 degradation products). The ANEC position paper built upon a series of research work funded by one of its members. As an example, ANEC calculated an

Table 5 is based on the literature 2015-2019, from this topic and shows the reported maximum average concentrations of compounds in **aerosols** from electronic cigarettes and for the most aggressive compounds. ANEC deals in majority with e-liquids and the compounds released by vaping could be identified in our table 5.

acceptable limit of about 1mg/ml e-liquid for benzaldehyde often used in cherry flavours based on an acceptable daily dose derived from a German indoor air limit and found that up to 21.2 mg/mL were measured (Tierney et al., 2015). One can discuss a long time about appropriate limits and appropriate risk assessment methods but it seems that this result is a clear indication that there may be a problem – assuming that benzaldehyde exposures do not become more healthy when intermittently inhaled and high peak exposures occur. In some cases only concentration ranges in e-liquids could be identified from safety data sheets. Nevertheless the calculated limits may be lower than the indicated concentration ranges. We stress that we consider our approach as a starting point for a more detailed and refined risk assessment but certainly appropriate to determine substances which may be of concern. Some of the calculated limits were clearly above measured concentrations suggesting that a limit may not be needed. As regards solvents ANEC considered that more discussion is needed before even tentative limits can be proposed. Anyway, we do not find it appropriate to put aside flavours altogether!

Page 56, lines 9-21: It is rather difficult to judge a study which has not been published. It is not a surprise that peak air concentrations during a puff "can be easily two orders of magnitude higher than the inhaled concentration of the general population". But this in itself does not rule out the possibility to make comparisons based on a daily inhaled dose for some effects. A distinction must be made between dose related (long-term) effects and concentration related (short-term) local effects. There is no reason why the former could not be assessed based on a daily dose calculated from a (suitable or modified) HBGV. In a letter to the editors Bos et al. have discussed the issue of the appropriate dose metric (Bos et al. Tobacco Induced Diseases (2016) 14:21): "The exposure assessment may either be an estimate of the pulmonary or alveolar concentration (if local effects are the endpoint of concern) or of the absorbed dose (in case systemic effects are of interest. And further: "As to systemic exposure, the dose taken up from one puff can easily be multiplied by the total daily number of puffs to estimate the total daily systemic dose". If this is accepted in principle that the daily dose is an appropriate

Bos et al was accepted for publication in Inhalation Toxicology. The reasoning in this comment is correct up to the point where it is suggested that a comparison can be made with health based guidance values, which are more reflecting continuous exposure over several hours per day in contrast to the discontinuous exposure pattern for e-cigarettes. The SCHEER therefore adopted the method of Visser et al based on inhalatory data, estimation of the maximum alveolar concentration for local effects and the total absorbed daily dose for systemic effects to arrive at the MoE (see Section 6.5.5.3) . MoE-values are shown in the text.

metric for certain effects than it is difficult to understand why comparisons with health based guidance values (HBGVs) which are often (but not always) related to continuous exposure lasting for hours per day and long term (particularly systemic) effects should not be suitable – being understood that the comparison is made on (...) please find further comments to different parts of p. 59 in paper attached.



ANEC-PT-2020-CEG-004ANEC_Comments

251	<p>Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU</p>	<p>6.5.5 Risk assessment</p>	<p>See our comment in the METHODOLOGY section, especially about what is a good risk assessment based on the SCENIHR (2012) guidelines (uploaded in the METHODOLOGY section). SCHEER failed to provide a good risk assessment per SCENIHR guidelines. It failed to include a comparison with other relevant risks (smoking for the most risky and everyday life risks for the least risky). It failed to use a risk benefit/cost benefit framework based on the real world where some people, including young people, are still smoking, nearly a quarter of the EU population, according to Eurobarometer data (cited by SCHEER).</p>	<p>For comparison with smoking: see Table 1, Answer 1. In addition: cost/benefit analyses is not in the ToR of this mandate.</p>
			<p>Page 56 / Line 9 The study cited by SCHEER is supposed to be “a review on toxicokinetics and dynamics of use of electronic cigarettes” but it appears as “Bos, P.M.J., Soeteman-Hernández, L.G. and Talhout, R. (2020). Risk assessment of smoke components: a pragmatic choice for dose metrics. To be published” in the REFERENCES section. The unpublished state of this study on smoke components doesn’t allow verification of whether there is anything pertinent to e-cigarette use (vaping) in it. The same study is cited two more times on the same page. Using unpublished evidence for risk assessment contradicts the SCHEER/SCENIHR guidelines on transparency.</p>	<p>Bos et al was accepted for publication in Inhalation Toxicology, Since there are no health based guidance values (HBGVs) for smoking or using electronic cigarettes and existing HBGVs such as occupational exposure limits in general are not applicable to the electronic cigarette intermittent use scenario, the SCHEER performed a risk assessment in which chemical-specific information that is relevant for the scenario (i.e., intensity, duration, and frequency) is taken into account. Because the available hazard information, often based on animal experiments, will mostly be obtained with an exposure regimen that also will significantly differ from the electronic cigarette use scenario, a direct comparison of exposure and hazard characteristics was considered not to be possible.</p>
			<p>Page 56 / Lines 52-54 The SCHEER based its risk assessment mainly on Viser et al., but failed to mention any risk comparison, especially between vaping and smoking when its main source of information does: “It may be</p>	<p>As a pragmatic alternative, the Margin of Exposure (MoE) approach was applied. This approach offers the possibility to take the specific exposure characteristics into account. See for more details Section 6.5.5.2 and 6.5.5.3. The overall conclusion on the risk remains based on the quantitative level of the MoE.</p>

			concluded that the health risks associated with smoking conventional cigarettes are considerably higher than those associated with using e-cigarettes. That conclusion assumes comparable usage patterns (a similar number of inhalations over a comparable period).”, Viser et al. 2015, Conclusions, page 43.		The SCHEER agrees. Text has been adapted.
			Page 57 / Line 28 Using “smokers of electronic cigarette” is misleading. It should be replaced with “electronic cigarette users” as defined in SCHEER’s own terminology, page 19.		Agreed and corrected.
252	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.5.5 Risk assessment	Page 58 / Lines 36-49 SCHEER cites various conclusions by Visser et al., 2019, but fails to include Visser’s risk comparison for nicotine systemic effects under real world conditions. Visser et al. found that the risk comparison for the nicotine systemic effects, even at the highest exposure level scenario, is comparable to 2 or 3 cups of coffee. Specifically, Visser et al. found: “Vaping and breathing behavior, the characteristics of e-cigarettes and the dimensions and rate of ventilation of the room all have a large bearing on the concentrations of chemicals to which bystanders are exposed. In the ‘car’ scenario, we considered a situation in which two people vape in a confined, unventilated space. The level of exposure in this scenario will approximate the highest levels that should occur in real life. In this scenario, bystanders may experience irritation of the respiratory tract as a result of exposure to propylene glycol and glycerol. If nicotine-containing e-liquid is used, systemic effects of nicotine can occur, including palpitations and an increase of the systolic blood pressure, comparable to what may be expected from the intake of the amount of caffeine contained in 2 or 3 cups of coffee. Furthermore, due to the presence of TSNAs in some liquids, an increased risk of tumors cannot be excluded. We believe the ‘office’ scenario to be more indicative of a typical level of exposure in real life. Health risks to bystanders were also identified in this scenario. While irritation of the respiratory tract is not expected, systemic effects of nicotine (palpitations, increased blood pressure) may be experienced. Only a limited number of e-cigarettes and e-liquids were used in this study, and significant differences exist between products. A large variability in the exhaled amounts of		For comparison with smoking: see Table 1, Answer 1. The SCHEER drew her own conclusion in Section 6.5.5.6 based on the conclusions of the Visser study in Section 6.5.5.3. Variability was acknowledged throughout the Opinion. The SCHEER agrees. It has been corrected.

chemicals was also observed between subjects using the same device and e-liquid, presumably due to differences in the individual vaping and breathing behavior of the volunteers. It would therefore be interesting to study the effects of vaping topology more extensively, as well as device design and e-liquid composition on the amount of exhaled chemicals in future studies.”

Page 60 / Line 17
Using “second-hand smoke from electronic cigarettes” is misleading. It doesn’t respect SCHEER’s own terminology as defined on page 19.

253 Woessner Julie, Internal Network of Nicotine Consumer Organizations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU

6.5.5 Risk assessment
Page 60 / Lines 38-47
We question why does the SCHEER cite a WHO report at the beginning of its own conclusion on the risk assessment? It should have been treated independently, as any other material in the previous pages. It has to be noted that, at the least, the WHO tries to assess the differential risks between vaping and smoking, which seems to be the right way to consider the problem. The SCHEER failed to compare the risks of vaping and smoking throughout its Opinion, despite the fact that the vast majority of users in Europe are smokers or past smokers according to Eurobarometer data (cited by SCHEER).

With regard to the comparison with smoking: see Table 1, Answer 1.

Page 60 / Lines 55-57
The SCHEER assesses the weight of evidence but doesn’t qualify the risk itself. It also lacks a comparison with high risk of local irritative damage to the respiratory tract, like smoking, and everyday life risks, like walking in a polluted street.

A fully quantitative risk assessment was not possible. Therefore SCHEER based the risk assessment on a weight-of-Evidence assessment including different lines of evidence. One of the lines of evidence for various endpoints is based on the estimation of the MoE, a semi-qualitative risk value.

Page 61 / Line 1
There is no distinction between different kinds of nicotine. For example, so-called nicotine salts are less irritating. It’s why they are used in NRTs to avoid skin irritation.

SCHEER has added a remark on this (“it is noted that nicotine salts are less irritating”)

Page 61 / Lines 2-4
Lack the mention that these “adverse effects” are minor and don’t impact health. Combined with the low incidence, it should lead to a low risk assessment.

It was not possible to conclude on the severity of irritation: a fully quantitative risk assessment was not possible and cumulative effects can be expected but also cannot be quantified.

			Page 61 / Lines 7-9	We ask the SCHEER to explain this line of evidence much better.	Please, see the conclusion (second bullet) of the Visser et al study in Section 6.5.5.3. SCHEER expanded this conclusion as well as the conclusion in 6.5.5.6.
			Page 61 / Lines 15-16	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself. It also lacks a comparison with high risk of long-term systemic effects on the cardiovascular system, like smoking, and everyday life risks, like drinking coffee.	See answer above on a similar comment.
			Page 61 / Lines 25-27	We ask the SCHEER to explain this line of evidence much better.	See answer above on a similar comment.
			Page 61 / Lines 29-32	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself.	
			Page 61 / Lines 46-49	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself.	
			Page 62 / Lines 17-18	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself.	
			Page 62 / Lines 27-29	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself.	
			Page 62 / Lines 36-37	The SCHEER assesses the weight of evidence but doesn't qualify the risk itself.	
254	Moiroud Jean, Fédération Interprofessionnelle de la Vape (FIVAPE), France	6.5.5 Risk assessment		P. 56, lines 53-56: this risk assessment is not relevant of the market as they found nitrosamines when it is said in Visser et al 2015: " a small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." P. 58, line 22: TSNA shouldn't be there. "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." (Visser et al).	See Table 1. answer 4.

- P. 58, lines 26-28: wrong condition: 50% retention isn't relevant with the literature <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/> >95% for nicotine, ~90% PV/VG realistic for all other component See Table 1 answer 4.
- P. 58, lines 48-49: TSNAs shouldn't be part of the analyse. "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids." (Visser et al.). "Considering that only a limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU." See Table 1, answer 4.
- P. 59, line 37: NNN and NNK are not relevant for the majority of e-liquids without tobacco extract. See Table 1, answer 4.
- P. 61, line 11: diacetyl should be regulated on its own as suggested by AFNOR X D90-300-2. This comment is not clear.
- P. 61, line 33: Nitrosamines come from tobacco extract present in a minority of e-cigarettes. Formaldehyde and acetaldehyde account for >95% of the contributions of organic compounds to cancer potencies in this EC subset. But they are mainly by dry puffs. See Table 1, answer 4
- P. 61, line 36: exposure to the nitrosamines are not relevant. Tobacco extract containing TSNA should be banned. See Table 1, answer 4
- P. 61, line 40: formaldehyde is generated mainly by dry puff.
- P. 62, line 30: the model considers a 50% transfer of nicotine from e-cig to the second-hand exposure when it is only 5%. See: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/> This statement is not substantiated by the literature.
See Table 1 answer 4.
- P. 62, lines 36-37: TNSA are unlikely to be found in a majority of liquid as they come from tobacco extracts. See Table 1, answer 4.
- Ref:

St Helen et al. (2016). Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/>

255 Compernelle Thomas, British American Tobacco, Belgium	6.5.5 Risk assessment	<p>Prioritisation (P55, LN27-53) is meant to be based on sections 6.5.3 and 6.5.4, yet the decision (P55, LN52) to focus only on the organic substances in Table 5 is not aligned with the discussions in either of those sections, see e.g. P37, LN5-8. In the risk assessment, the report relies solely on the maximum levels measured in aerosol from a single, non-peer reviewed, study using pre-TPD2 products (1,2) with little relevance to current products in the EU. This study does not appear to address the potential background contribution to aerosol levels, the importance of which has been published on (3,4), and thus very likely overestimates results.</p> <p>P55, LN17-19 indicate how crucial choices of PoD studies and exposure estimates are, yet reasons for the choices made are not provided. Instead, in 6.5.5.3, the report refers to a single, non-peer reviewed study (1,2). This is an inappropriate study on several counts. Firstly, the exposure scenarios used do not correlate well with those described in 6.5.1 of the SCHEER report. Secondly, it relies on a single, unpublished, pre-TPD2 survey of 456 users, ignoring the wealth of data available in the literature, some of which is described in section 6.5.2.1, but not used in the risk assessment. Thirdly, it estimates peak alveolar doses for local effects. Literature quoted in the SCHEER report indicate most e-liquid aerosol is deposited in the tracheobroncheal tract. Additionally, animal studies and human experience show the main local effect is mild upper respiratory tract irritation that requires sustained exposure before manifestation. Average concentrations over time in the upper respiratory tract are thus the most relevant exposure measure. Furthermore, the assumed low absorption rate of 30% results in cumulatively increased alveolar estimates and is in contrast to data available on the main components, nicotine, PG and glycerol, and the study authors statements on aldehydes (p.55 in Visser et al 2016 (5)), all indicating rapid absorption from the respiratory tract.</p> <p>Overall the study significantly overestimates exposure, which leads</p>	<p>Probably this comment refers to the metals mentioned in Table 5. As stated, priority was given to substances frequently found in screened literature, substances with highest measured concentrations and substances with identified (low) thresholds.</p> <p>This is explained in Section 6.5.5.2 and 6.5.5.3. The Visser studies are the only experimental studies available with controlled conditions and realistic use topography, whereas the risks are estimated using the MoE approach. Other risk assessments predominantly compare exposure levels of substances in aerosol from electronic cigarettes with health based guidance values and this approach is considered less suitable since these ignore the toxicokinetics and dynamic of e-cigarette use as explained in Section 6.5.5.2. The potential background contributions in the literature sources cited do not include the priority substances in aerosol and are hardly relevant for the substances measured in the Visser studies.</p> <p>Thank you for this comment. All values of the MoEs are reported by SCHEER as well as the conclusions from the authors based on these MoEs. PoDs can easily be recovered from the literature cited. Regarding the value of the (published) Visser studies: see above.</p> <p>The risk assessment is based on the highest median aerosol concentrations for local effects and daily doses for systemic effects. Unfortunately, the comment does not refer to literature showing that “average concentrations over time in the upper respiratory tract are thus the most relevant exposure measure”. The 30% absorption rate indeed is conservatively chosen in the absence of reliable absorption studies.</p>
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to the conclusion (P58, LN7-8) that “Carcinogenic effects can be expected to occur due to exposures to nitrosamines and formaldehyde.” No attempt is made to contextualise this theoretical approach with published clinical biomarker data. In long term use of electronic cigarettes, biomarkers for nicotine, TSNAs and VOCs were compared to that of NRT, demonstrating TSNAs and VOC exposure was no different, or lower than, that of NRT use (6). This is consistent with the large body of biomarker work, not referred to at all in the SCHEER report, that consistently shows rapid reductions in exposures to TSNAs and VOCs when switching from smoking to electronic cigarettes⁷⁻¹³. Based on clinical data, carcinogenicity risks from these compounds is thus likely to be low, potentially comparable to that from long term NRT use.

With regard to TSNAs: see Table 1, Answer 4.

The supposed risk of local damage from exposure to polyols, aldehydes and nicotine (P60, LN55-P61, LN13) is partially based on the false premises that these substances are all irritants. By far the biggest contributors to the aerosol are propylene glycol and glycerol, both of which have been reviewed by several expert groups and not identified as irritants (14-18). They are used as solvents in (inhalation) medicinal and cosmetic applications precisely because of their tissue compatible nature. The “line of evidence” that cohort studies consistently demonstrate mouth and throat irritation dissipates over time, is contrary to the suggestion of cumulative irritation leading to damage over time. The flaws in the study (2) leading to the overestimation of exposures of nicotine (P61, LN7-9) and aldehydes (LN10-13) have been described above.

With regard to carriers/PG, please see reply to comment 153.



C1R0-6.5.5_Risk_Assessment-References_1

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Tobacco, Belgium

6.5.5 Risk
assessment

The discussion favouring the use of MoE (6.5.5.2) is based on the false premises that data from a more continuous exposure scenario is not applicable to e-cigarette use. Applicability depends on the toxic effect of concern. Both animal studies and human data suggest an absence of acute effects mediated by peak exposure. The uncertainty is around potential effects from sustained exposures. For this, average exposure concentrations over time, and therewith HBGV and animal inhalation set ups, are appropriate. Additionally,

The SCHEER disagrees with the view that studies using a continuous exposure are directly applicable to the e-cigarette exposure scenarios as explained in Section 6.5.5.2. HBGVs are more intended for continuous exposure scenarios and definitely do not cover peak exposures. And this is the reason that the SCHEER relies on comparison with HBGVs for second-hand exposure. For direct exposure the SCHEER acknowledges that HBGVs can be applied if the assessment shows “that the puff concentrations measured are below these

HBGV are intended for various scenarios, including peak exposures, e.g. air pollution, with mainly low exposure to the general public in inside environments and short peak sessions, e.g. when walking along busy roads. Indeed, the SCHEER report itself actually does rely on comparisons to HBGV, e.g. in its metal assessments (for example, P15, LN38). And yet it uses this flawed rationale to dismiss multiple published assessments from various sources including the US National Academies of Sciences, Engineering, and Medicine and Public Health England (P58, LN55-P59, LN4).

The 2nd hand exposure section P58, LN13-49, relies on a single study, referenced twice (1,2), where the approach to estimating exposure via exhaled breath is inaccurate. More accurate methods would be to use direct air concentration measurements or biomarkers of exposure in the bystanders, such as done in several publications that have been referenced in discussions in the SCHEER report, but then not taken into account for the actual risk assessment. Not only is the method suboptimal to address bystander exposure, additionally, the exposure scenarios assumed are unrealistically high compared to the exposures assumed in the SCHEER report for the main user risk assessment. A more credible 2020 assessment from the UK Committee on Toxicity (3) concludes “E(N)NDS use is associated with some emissions into ambient air, including nicotine. For most health effects, the risks to bystanders will probably be low in conventional exposure scenarios, although pharmacological effects from exposure to nicotine in ambient air may occur in some individuals.”

The conclusion on respiratory tract carcinogenicity due to nitrosamines and some VOCs exposure misleadingly states the human data is very limited and does not allow a conclusion (P61, LN35). However, that is because the SCHEER report does not include reference to any of the clinical biomarkers of exposure study data that exist, demonstrating exposures to nitrosamines and some VOCs from electronic cigarette use are low (4-9) and comparable to those from NRT (10).

The conclusion in 6.5.5.6 that the evidence base for cardiovascular effects for main users is strong, is inconsistent with the lack of long-

standards and therefore clearly point at the absence of any risk with a wide margin” (Section 6.5.5.4). The SCHEER objects to the view that this is a “flawed rationale”. The assessments of US NAS and PHE are not dismissed, but critically assessed and cited frequently.

While the SCHEER’s conclusion regarding second hand exposure actually is not far from what is concluded in this comment it is not clear why the method applied is considered inaccurate. No reason is given why the exposure scenarios assumed are unrealistically high.

Thank you for pointing this out. The SCHEER reviewed the literature and added data where deemed relevant and within the literature selection criteria.

Buchanan et al conclude that the impact of chronic e-cigarette exposure is essentially unstudied. And: overall, data suggest that exposure to e-cigarettes could be a potential cardiovascular health concern.

term data identified in 6.5.4. And where longitudinal studies do exist, following cardiovascular health aspects of vaping, these indicate an improvement in cardiovascular health when switching from vaping (11-14), as reviewed in Buchanan et al. (15) The remaining lines of evidence relate only to nicotine exposure. Nicotine exposure to electronic cigarettes is broadly comparable to that from nicotine replacement product (e.g. 6-month biomarker data (10)), and thus, if the main CVD risk arises from the nicotine exposure, nicotine-related CVD risk from vaping would be expected to be comparable to that from NRT. For conclusions on risk for the user, it should be considered that the vast majority of EU regular users are smokers or ex-smokers (16-19). Therefore, the relative risk versus smoking and resultant harm reduction should be an important consideration.

For comparison with smoking: see Table 1, answer 1.



C2R0-6.5.5_Risk_Assessment-References_f

257	No agreement to disclose personal data	6.5.5 Risk assessment	P.57, 125: The conclusions of the Opinion lack a valid comparison with traditional cigarettes, particularly with regard to the health effects on users.	See Table 1, answer 1.												
258	Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.5.5 Risk assessment	<p>P57/</p> <table border="1"> <tr> <td>P</td> <td>59/</td> <td>L</td> <td>23</td> <td>-</td> <td>L28</td> </tr> <tr> <td>P</td> <td>60</td> <td>-</td> <td>61/</td> <td>L</td> <td>55 - 13</td> </tr> </table> <p> Risk_assessment.pdf</p>	P	59/	L	23	-	L28	P	60	-	61/	L	55 - 13	<p>Comment 1: see Table 1, Answer 1. The problem formulation is based on the ToR of the Commission's mandate in Section 2.</p> <p>Comment 2: see Table 1, answer 1.</p> <p>Comment 3: The SCHEER agrees. Corrected.</p> <p>Comment 4: see Table 1, answer 1.</p> <p>Comment 5: see Table 1, answer 1.</p>
P	59/	L	23	-	L28											
P	60	-	61/	L	55 - 13											
259	Robson Deborah, King's College London, United Kingdom	6.5.5 Risk assessment	<p>Page 55 – lines 17-53; page 56, lines 3-57; page 56, line 1-56; page 57, lines 1-57; page 58, lines 1-57; pages 59- lines 1-57; page 60, lines 1-57; page 61, lines 1-57; page 62, lines 1-42</p> <p>Regarding the impact of the use of e-cigarettes on health, it is not clear from the preliminary Opinion if and how the relative harm of e-cigarettes, in comparison to the harm caused by combustible cigarettes was assessed. Nor is it clearly communicated if</p>	See Table 1, answer 1.												

comparisons are made with occupational health and safety exposure standards. Given the vast majority of e-cigarette users are current or former smokers and only a very small proportion of people in the EU who vape have never smoked, and the main reasons for vaping are to stop or reduce smoking, knowing the relative risks, as well as the absolute risks are important. Also, further clarity is required about communicating the presence and levels of toxicants in the bodies of people who use e-cigarettes, in comparison with smokers (or before and after people switch from smoking to vaping) and what relevance and significance this has on human health. We draw the Committee's attention to chapter 9, specifically pages 163 to 171 of McNeill A, Brose LS, Calder R, Bauld L & Robson D (2018). Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England, about the health risks of e-cigarette use and comparison of studies that assessed biomarkers of exposure in e-cigarette users relative to smoking.

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Patients'
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6.5.5 Risk
assessment

Given that everyone spends the vast majority of their time inside, second-hand smoke directly affects indoor air quality. Whether it is pollution from e-cigarettes or from tobacco smoke, they all affect the air we breathe in and should be prevented by applying the 100% smoke free environments, agreed on Article 8 of the WHO Framework Convention on Tobacco Control.

Studies have shown that e-cigarettes have the ability to degrade indoor air quality, putting bystanders at risk of second-hand exposure (Li, 2020) . This is due to high concentrations of particulate matter resulting from the use of e-cigarettes, while studies suggest potential respiratory and cardiovascular effects from e-cigarette aerosols.

We believe the recent evidence from EU-funded research project 'Tackling second-hand tobacco smoke' (TackSHS) should be included in this opinion (page 58, lines 13-49), as it examined passive exposure to e-cigarette emissions and demonstrated an increased risk for respiratory health, including in certain inflammatory biomarkers (Tzortzi, 2018) .
Ref:

Thank you for sharing your thoughts. This is outside the mandate for SCHEER in this Opinion.

Thank you for pointing out this reference. SCHEER has evaluated this review.

The results of the TackSHS study regarding exposure were included in Section 6.5.2.2 (second-hand exposure). The SCHEER has evaluated the reference suggested and included it in Section 6.5.4 acute effects)

Li et al (2020). Effects of Electronic Cigarettes on Indoor Air Quality and Health. <https://doi.org/10.1146/annurev-publhealth040119-094043>

Tzortzi (2018). Passive exposure to e-cigarette emissions: Immediate respiratory effects. *Tob. Prev. Cessation* 2018;4(May):18 <https://doi.org/10.18332/tpc/89977>

261	Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.5.5 Risk assessment	<p>Line # n/a</p> <p>It is striking that no serious attempt to compare the risk of e-cigarette use to smoking is undertaken in the review. Given that the target market is adult smokers, this comparison is necessary to understand the potential benefits of e-cigarettes for that part of the population.</p> <p>The failure to do so constitutes a divergence from the principles contained on p38 of the SCHEER guidance on Weight of Evidence (2018) to which the report is supposed to adhere. That guidance notes that “problem formulation should be purpose-oriented and conducted with the correct understanding of the relevant questions”. It is difficult to understand why the report does not consider the comparison of harm from e-cigarettes with combustible tobacco as a relevant question given the obvious relationship between the two.</p> <p>n/a</p> <p>McNeil et al (2018) (*1) is cited concerning the lack of evidence for specific harms from particular flavoring substances. However, the key finding of PHE, that e-cigarette use is likely to be around 95% safer than smoking cigarettes, is omitted. This finding, from a well respected public health body, should be taken into account as part of the narrative report and given weight in the scientific opinion, where currently it is not.</p> <p>We attach the 2015 PHE (*2) evidence review where this was first announced and note that the 2018 report cited upholds this estimate: “...stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously.”</p> <p>P57/ L28</p> <p>Referring to “smokers of electronic cigarettes” is incorrect since e-cigarettes do not combust. Moreover, it is contradictory to the statement of the Committee on terminology (page 19; lines 47-55).</p> <p>P 59/ L 23 - 40</p>
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With regard to the comparison with smoking: see Table 1, answer 1.

Stephens et al (2018) is cited in order to substantiate the source and scale of any potential carcinogenic risks from an electronic cigarette. However, the report completely ignores the central objective of this study, made clear in its title: “Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke” The central finding of this study is that e-cigarette users are typically exposed to 0.4% of the lifetime cancer risk of smokers, but this finding does not seem to have been considered in the SCHEER report despite the committee having read the study. It is clearly relevant to the risk assessment and should be included in the narrative as well as considered in the scientific opinion.

P 60 - 61/ L 55 - 13

The risks of irritative damage to the respiratory tract are not placed in the context of the comparable risks associated with smoking. This leads the SCHEER to characterize a risk that applies to never-smoking users who, according to Eurobarometer data, make up a tiny fraction of total users of e-cigarettes in Europe. A number of studies show that for smokers, there is a significant benefit to the respiratory system in those who switch to e-cigarette use.

Polosa (2014) (*3) undertook an examination of asthmatics who had switched - either completely or partially - to e-cigarette use from smoking. The study concluded: “Overall there were significant improvements in spirometry data, asthma control, and AHR. No severe adverse events were noted. This small retrospective study indicates that regular use of e-cigs to substitute smoking is associated with objective and subjective improvements in asthma outcomes. Considering that e-cig use is reportedly less harmful than conventional smoking and can lead to reduced cigarette consumption with subsequent improvements in asthma outcomes, this study shows that e-cigs can be a valid option for asthmatic patients who cannot quit smoking by other methods.”

Ref:

* 1-
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf

			<p>* https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733022/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf</p> <p>* 3- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4053879/</p>	
262	Saboga-Nunes Luis, EUPHA-HP, Portugal	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>This SCHEER Preliminary Opinion on electronic cigarettes is a relevant comprehensive and updated tool where three suggestions are suggested</p> <p>1) Although in chapter 6.6. the topic is introduced, the strategy of the nicotine delivery industry to proceed to the renormalization of cigarette smoking by bypassing WHO tobacco control framework should be more expanded. For example this issue could be introduced earlier in 6.5. and more broadly</p> <p>2) There is not enough strength regarding the argument of addiction (to electronic cigarettes) per se, and this contradicts a health promotion strategy to the issue. Therefore the SCHEER Preliminary Opinion on electronic cigarettes focus extensively in the risk perspective - that is overwhelming important - but should also consider the problem by the health promotion perspective to highlight several aspects of public health, Equity, Public participation, Empowerment, Intersectoriality and Sustainability. An overall discussion on the "modus faciendi" (scientific theories to address the issue) is missing.</p> <p>3) The health literacy perspective is missing as one of the structural approaches to deal with the issue of renormalization and public awareness</p> <p>Ref: Luis Saboga-Nunes, Diane Levin-Zamir, Vance Rabiuis, Tobacco still a major killer—will we achieve the end game?, European Journal of Public Health, Volume 27, Issue suppl_4, October 2017, Pages 22–25, https://doi.org/10.1093/eurpub/ckx161; Saboga-Nunes L, Bittlingmayer UH, Okan O. Salutogenesis and health literacy: the health promotion simplex! In: Okan, O., Bauer, U., Levin-Zamir, D., Pinheiro, P., Sørensen, K. (eds.) (2019). International Handbook of Health Literacy. Research, practice and policy across the lifespan. Bristol: The Policy Press, University of Bristol, England (U.K.)</p>	<p>Thank you for your comment.</p> <p>The aspects addressed in this comment are outside of the scope of the Opinion.</p>
263	Spina Francesco, private, Italy	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Page 65 . Line Nrs 41 to 50</p> <p>Data extracted from the "Special Eurobarometer 458" is old (2017) and obsolete.</p> <p>At June 2020 vaping nontobacco flavors was no more associated with youth smoking initiation than vaping tobacco-flavors (AOR in youth, 0.66; 95% CI, 0.16-2.76; P = .56) but vaping nontobacco</p>	<p>See Table 1, answer 11.</p>

			<p>flavors was associated with increased adult smoking cessation. see attached study. Page 65 line numbers 39-40 There is a clear evidence that to quit smoking the best way is to stay away from tobacco but using nontobacco flavours is the most effective way as proved by the attached study, flavour restrictions will only lead to make people go back to smoking cigarettes, not perceiveng a real difference or satisfaction. Ref: Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation Abigail S.Friedman,Ph D;Si Qing Xu,BS JAMA Network Open.2020; 3(6):e203826. doi:10.1001/jamanetworkopen.2020.3826</p>	
264	Albrecht Hans-Peter,Interessengemeinschaft Elektronisches Dampfen (IG-ED),Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>p.63, ll.26-28: Restriction/Prohibition of flavors won't lead to abstinence, just to purchases from new and questionable sources or -worst case- may lead adults and youth who have already smoked back to smoking for good. There is no reason to“protect“ youth from „attractive“ flavours by limiting access to them for adults: A new analysis of data from the 2019 National Youth Tobacco Survey (NYTS), released last week by the Centers for Disease Control and Prevention (CDC) and the FDA, shows that flavors are definitely not the main reason kids vape. The top spot belongs to curiosity. Among the teens who were surveyed, 56.1 percent listed curiosity as a reason they tried e-cigarettes. That was more than double the next most popular reason, “friend or family member used them” (23.9 percent). (In the lower middlefield: flavours)</p>	See Table 1, answer 7.
265	Albrecht Hans-Peter, Interessengemeinschaft Elektronisches Dampfen (IG-ED), Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>p. 63, ll.19 : “current use” in real life is either “daily use”or “4-5 days per week”(but e.g. not once in the last 30 days. UK: Data from the 2019 ASH YouGov Smokefree youth GB survey³⁴ suggest that while some young people, particularly those who have tried smoking, experiment with e-cigarettes, regular use remains low. Regular use of e-cigarettes remains largely confined to current or ex-smokers. Not a single never smoker reported vaping daily and only 0.1% vaped more than once a week.</p>	Thank you for your comment.
266	Jarvis Martin,University	6.6 Role in the initiation of smoking	<p>page 63, lines 5-8 page 67, lines 12-45</p>	

College London, United Kingdom (particularly focusing on young people)

page 68, lines 36-39
page 70, lines 12-13
SCHEER have adopted a simplistic version of the gateway hypothesis, whereby use of e-cigarettes by never tobacco users followed by uptake of cigarette smoking is taken as evidence of a causal gateway effect. This is a post hoc ergo propter hoc argument, in which it is assumed that in the absence of prior trying of e-cigarettes, uptake of cigarettes would not have occurred. The report makes no reference to the “common liability” or “shared risk” explanatory framework for clustering of risk behaviours, which takes account of the fact that a variety of influences (genetic, familial, social) act on individuals to confer a higher propensity to engage in risky behaviours, including both cigarette smoking and use of e-cigarettes (1). Thus young people who come from homes with adult tobacco users, or who truant from school, or who use marijuana and other drugs, or who have experienced bullying at school, are more likely to smoke cigarettes or to use e-cigarettes (2). Which product comes first in their use career may be determined largely by chance, opportunity or zeitgeist. A recent genetic epidemiology study employing Mendelian randomisation techniques to examine polygenic risk scores for smoking initiation concluded “Our results indicate that there may be a shared genetic aetiology between smoking and e-cigarette use, and also with socioeconomic position, externalising disorders in childhood, and risky behaviour more generally. Taken together, this indicates that there may be a common genetic vulnerability to both smoking and e-cigarette use, which may reflect a broad risk-taking phenotype” (3).
There are two meta-analyses of the association of e-cigarette use in never smokers with subsequent cigarette uptake that are more recent than those cited in the SCHEER report. Both confirm the positive association observed by SCHEER, but both draw attention to the common liability explanatory framework for the findings and caution against the gateway interpretation (4,5).
Two recent studies have employed propensity matching techniques to examine the relationship between e-cigarette use and subsequent cigarette smoking (6,7). Neither study’s results confirmed the gateway hypothesis; rather, their findings lent support to the importance of shared risk factors. A real world test of the gateway hypothesis espoused by SCHEER is provided by examining trends in population use of cigarettes over time as the popularity of e-cigarettes has grown. The SCHEER report refers to Levy et al. (2019)(8) who noted a decline in past 30-day smoking prevalence among US adolescents between 2014-2017, a period coinciding with the timeframe of electronic cigarette proliferation in the US. A further study from Levy (9), which examined the SimSmoke model, found that rather than increasing smoking, the popularity of e-cigarettes from 2013

See Table 1, answer 5.

onwards in England made a substantial contribution to reducing cigarette smoking prevalence among young adults aged 18-24. Another modelling paper, which analysed survey data on adolescents in the USA concluded: “Electronic cigarettes may have offset conventional smoking among US adolescents between 2010 and 2018 by maintaining the total nicotine use prevalence and diverting them from more harmful conventional smoking.” In summary, the SCHEER conclusion that there is strong evidence that electronic cigarettes are a gateway to smoking for young people is unsound. The causal gateway hypothesis provides an inadequate explanatory framework and is not well supported by evidence. In addition, data from monitoring of population smoking prevalence do not indicate any effect of the availability of e-cigarettes on increasing cigarette prevalence. Rather they may have contributed to cigarettes’ decline.



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<p>267 Hanewinkel Reiner, Institut für Therapie- und Gesundheitsforschung, Germany</p>	<p>6.6 Role in the initiation of smoking (particularly focusing on young people)</p>	<p>I want to add a paragraph to the section "gateway", with new publications and a new meta-analysis not presented in the text so far.</p> <p>The most comprehensive meta-analysis to date has been published in March 2020 (Khouja, Suddell, Peters, Taylor, & Munafo, 2020). This analysis convincingly shows that youth and young adults (up to age 30) who initiate nicotine use with e-cigarettes are much more likely to be smoking cigarettes later. The paper includes 17 studies from the US, UK, Mexico, Germany, and the Netherlands. Every single one of these studies showed that e-cigarette use was associated with significantly increased odds of subsequent cigarette smoking initiation. The paper includes impressive sensitivity analysis that presents analyses of unadjusted and adjusted odds (for a wide range of potential confounders) of subsequent smoking, how e-cigarette use and smoking were assessed, where the studies were done (US, UK, other countries), and whether or not studies included only youth (<18 years old) or young adults (18+ years old). While these different analyses led to slightly different overall estimates of risk, the results were always statistically significant and positive. The fact that the results are so consistent despite how the data are subdivided provides strong evidence that the association is real. The sub-analysis of the UK studies (aOR 3.85, 95% CI 2.18-6.81) is especially impressive and shows similar risks as for the US studies (aOR 2.95, 95% CI 2.14-4.06). Other cohort studies with participants from Member States of the European Union besides the UK have been conducted in Finland (Kinnunen et al., 2019), the Netherlands (Treur, Rozema, Mathijssen, van Oers, & Vink, 2018), Romania (Penzes et al., 2018), and Germany (Hansen, Janssen, Morgenstern, & Hanewinkel, 2020; Morgenstern, Nies, Goecke, &</p>	<p>Please see Table 1, answer 5.</p>
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Hanewinkel, 2018). All these further studies confirm that earlier e-cigarette use is an independent risk factor for later use of conventional cigarettes. Taken together, the results of these European studies give evidence for a gateway effect of e-cigarettes which is not a unique US phenomenon, but also present in Europe.



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268	Ollila Eeva, Cancer Society of Finland, Finland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>The SCHEER opinion concludes that flavours are a crucial factor for the adolescents to initiate e-cigarette use. Furthermore it is noted that adolescents like tobacco flavour less than sweet and other “youth-appelling” flavours, while concurrent or ex-smokers like also tobacco flavour. There is clear evidence that e-cigarettes serve as a gateway for smoking. It is clear from the SCHEER preliminary opinion that use of e-cigarettes has increased markedly among adolescents and that youth appealing flavours play a critical role in initiation. Findings also from a Finnish longitudinal youth study suggest that experimentation with nicotine e-cigarettes serves as a gateway to subsequent use of conventional cigarettes as well as nicotine e-cigarettes (Kinnunen et al. 2019). The data in the opinion shows that among the flavours that appeal to smokers is tobacco flavour, a flavour not appealing to adolescents without a history of smoking. Tobacco flavour is among the flavours appealing to smokers, but it is not appealing to non-smoking adolescents. It is furthermore clear from the opinion that e-cigarettes are not very successful as a cessation tool for smokers.</p> <p>Kinnunen JM, Ollila H, Minkkinen J, Lindfors PL, Timberlake DS, Rimpelä AH. Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: A longitudinal study among Finnish adolescents. <i>Drug Alcohol Depend.</i> 2019 Aug 1;201:182-187. doi: 10.1016/j.drugalcdep.2019.04.019. Epub 2019 Jun 19. PMID: 31238240</p>	See Table 1, answers 7 and 6.
269	Loucas Nancy, Coalition of Asia Pacific Tobacco	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Whilst SCHEER acknowledges most studies they include are from USA, there is enough evidence from the Europe to address the issue from a European context. It is disingenous to cherry pick statistics to suit a confirmational bias in such a wide reaching public health endeavor. There are vast differences in regulatory frameworks, product availability and the collection and assessment of data.</p>	The SCHEER agrees that a high prevalence of daily use is more concerning than a high prevalence of ever use, as not all ever users will continue to daily users. Still, some of them do, and therefore data on ever use are also informative.

smoking ritual and makes it easier for former smokers to stay away from cigarettes. Moreover, The 2018 U.S. National Academies of Sciences, Engineering, and Medicine Report [3] found that the smoking rate has decreased overall more rapidly since vaping became more prominent in the United States. The researchers concluded: “The inverse relationship between vaping and smoking was robust across different data sets for both youth and young adults and for current and more established smoking.

References:

[1] Friedman AS, Xu S. Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. *JAMA Netw Open.* 2020;3(6):e203826.

[2] David Clement, Yaël Ossowski, Michael Landl, Why Vape Flavours Matter

[3] Levy DT, Warner KE, Cummings KM, et al Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check *Tobacco Control* 2019;

271 Martinez Javier, JT International SA, Switzerland
6.6 Role in the initiation of smoking (particularly focusing on young people)

P.62, 1.51-53 SCHEER states, that “US data may not necessarily reflect the exact situation in the EU...”. However, the US and EU incontestably do not “reflect” the same situation or conditions. The current statement implies similarities between US and EU whereas they differ on several important issues, e.g., regulations, product availability, brand market shares. Please replace “may not necessarily” with “do not”.

The Opinion has been changed accordingly.

P.67, 1.20-24 The “renormalisation hypothesis” is inconsistent with recent data on smoking prevalence, which indicate that smoking prevalence is decreasing (Wang et al 2018) See also Hallingberg, et al., 2019.

Thank you for your comment.

P.67, 1.26 Please amend the statement, “Overall, the SCHEER is of the opinion that there is strong evidence that electronic cigarettes are a gateway to smoking for young people.” As the SCHEER notes, “there is limited national or regional evidence using population based cross sectional or cohort studies.” How, based on such limited evidence, could SCHEER reach a conclusion to a “strong evidence”? On the one hand, the SCHEER totally dismisses the conclusions from studies questioning the gateway to smoking, e.g., Lee et al. (2018c) or Levy et al. (2019), based on the fact that “the studies used in the above meta-analyses and reviews are predominantly from the US and other non-European Union countries.” On the other hand, the SCHEER relies heavily on other

Please see Table 1, answer 5.

US-based studies to opine on an association between e-cigarette use and cigarette smoking among adolescents and young adults. SCHEER fails to comment on a crucial point, i.e., use can be described with different measures. Ever use is a common measure reflecting lifetime use, including even just once or twice. While past 30-day use describes recent use, it is not necessarily reflective of continuous use. The study authored by Soneji et al. 2017 does not allow causation to be inferred. Although this study suggested that teen vaping was associated with later experimentation of smoking, this does not prove that vaping caused the smoking. Please remove any causation-related insinuation, especially when seeking epidemiologic associations where confounding is large and complex in its causes. Etter 2018 concluded, “most of the evidence that should be considered before deciding whether an association is causal have either not been met or are not documented in the case of the claim that e-cigarettes can be a cause of cigarette smoking. The gateway hypothesis cannot currently be either accepted or confidently refuted because the evidence for it is scarce and inconclusive.” Please refer to a subsequent erratum of the Soneji study indicating a significantly reduced pooled unadjusted odds ratio of cigarette smoking initiation by ever e-cigarette use. The analysis of the ‘gateway’ literature (Lee et al., 2018c) cited by the SCHEER highlights that there was no evidence from the studies reviewed that adolescents were regular e-cigarette users at baseline, and no evidence that they were smoking cigarettes regularly at follow-up. Lee et al. found that none of the studies purporting to demonstrate a gateway effect were adequately adjusted for confounding factors. SCHEER ignored a subsequent analysis by Lee et al. (2019) cautioning about incomplete adjustment for confounding and concluding that “our results do not unequivocally demonstrate that any true effect exists.” Strong evidence contrasting the notion of a “gateway” effect for e-cigarettes emanate from smoking prevalence data indicating that youth smoking rates have declined rapidly in the UK and US since the introduction of vaping, making it very unlikely that vaping is increasing youth smoking. (Wang et al.2020, Mendelsohn & Hall 2020)

Ref:

Etter (2018). Gateway effects and electronic cigarettes

Hallingberg (2020). Have e-cigarettes renormalised or displaced youth smoking

			<p>Lee (2019). Investigating gateway effects using the PATH study</p> <p>Mendelsohn (2020). Does the gateway theory justify a ban on nicotine vaping in Australia</p> <p>Soneji (2018). Errors in data input in meta-analysis on association between initial use of e-cigarettes and subsequent cigarette smoking</p> <p>Wang (2020). E-cigarette use among middle and high school students.</p>	
272	Ross Louise, National Centre for Smoking Cessation and Training, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>12-13</p> <p>This is deeply illogical. There is very weak evidence that e-cigarettes act as a gateway to youth smoking. Counting numbers of youth who have tried vaping (young people try all sorts of things) is very different to counting those who are regulars users. In countries where there is sensible regulation and advertising controls, and where vaping is encouraged as an option for adults who want to stop smoking, there is a notable reduction in youth smoking.</p> <p>Additionally, as a clinical practitioner who has dealt with young people who have been smoking since the age of 10 or 11, who have mental health issues, have been through the youth criminal justice system or who are in care, I would see a young person's use of a vape instead of a smoked cigarette as a health benefit.</p>	Please see table 1 answer 5.
273	Poirson Philippe, France	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>[p. 63 l. 5-6] SCHEER states that US data "leads to concern that electronic cigarettes may be exposing a significant number of youth to nicotine". However, the referenced studies do not distinguish between use with or without nicotine. On this basis, it is not possible to say what is the real proportion of American youths exposed respectively to nicotine, cannabinoids or flavour-only vaping.</p> <p>Moreover, the American criterion of use within 30 days does not distinguish different types of use between frequent or occasional use. In particular, occasional use can be to respond to peer pressure (e.g. in party) to avoid smoking. Use with cannabinoids can be instead of smoked cannabis, etc. In the absence of clear, precise and sensitive distinctions, the American data presented are of very low epistemic value. Jarvis et al. (2020) have shown that frequent vaping use concerns only 1-2% of American youth without tobacco use.</p> <p>The SCHEER report claims that "most e-liquid brands are available in a variety of youth-appealing flavours". In the Hoffman et al. 2016</p>	<p>This is why the SCHEER phrases it as concern. No change needed.</p> <p>There is no causal theory expressed by the SCHEER on this.</p>

study cited (p. 64), it is stated that "also, Coldwell et al. concluded that 'change in sugar preference from high to low during adolescence appears to be associated with the cessation of growth'". This tendency to reduce the attractiveness of sweet tastes during adolescence does not correspond to the causal theory asserted by the SCHEER.

[p. 67 l. 34] The SCHEER states (p.19 l.21-22) "For each line of evidence, the criteria of validity, reliability and relevance need to be applied and the overall quality has to be assessed". However, 6 out of 7 studies in the meta-analysis of Soneji et al. present critical or serious shortcomings. In particular, these 6 studies do not take into account the factor of smoking by relatives, which is the predominant risk factor in youth smoking. This deficiency removes all credibility from these studies. Moreover, several of them suffer from other biases: poorly evaluated cofactors, small panels, very high attrition rate. As Gary Chan et al. 2020 point out it is not possible to consider the evidence presented as valid. In addition, Soneji et al. has a self-complacency bias with several study authors in the meta-analysis writing group. It seems unethical to be judgmental and judged and to be self-satisfied (Kruger-Dunning, 1999).

The documents referenced by SCHEER fail to prove a causal gateway effect, a fortiori in the European environment, which is very different from that of the United States. The SCHEER draft ignored a study by the Observatoire Français des Drogues et Toxicomanies (OFDT) which presents a very robust methodology, a large panel and which is in a context under European regulation. The results of Chyderiotis et al. show that "among ever-smokers, adolescents who declared having ever used e-cigarettes were less likely than those who did not to transition to daily smoking at 17: RR = 0.62 95%CI [0.60 - 0.64]. We found similar results for those who experimented with e-cigarettes before initiating smoking, RR = 0.76 95%CI [0.66 - 0.89]". These results provide indication of a possible diverting effect of vaping against smoking in youth (Levy 2019, Foxon 2020). As the bad experience of San Francisco ban on vaping flavour

Please see Table 1, answers 5 and 8.

			shows (Yang 2020), there's a risk of sustaining young smoking with bad anti-vape regulations. The SCHEER draft fails to give a clear picture of the subject. SCHEER should revise its analysis to address the issue in a scientific manner by reviewing data on common vulnerability factors rather than a causal approach that is implausible and without epistemic value.	
274	Champagne Maxime, Phoebe, France	6.6 Role in the initiation of smoking (particularly focusing on young people)	p64 Flavours. The role of flavor in smoking cessation shouldn't be avoided This study should be considered in this part: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787 "Relative to vaping tobacco flavors, vaping nontobacco-flavored e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation.	See table 1, answer 7.
275	Champagne Maxime, Phoebe, France	6.6 Role in the initiation of smoking (particularly focusing on young people)	p70 lines 12-15 "Overall, the SCHEER is of the opinion that there is strong evidence that electronic cigarettes are a gateway to smoking for young people." This statement need to be less partial, US studies aren't relevant in the EU (nicotine content, advertisement, TPD implementations) and taking in count of local European studies; revealing a strong decrease in youth smoking https://www.sciencedirect.com/science/article/pii/S0376871620300181#Highlights Conclusions Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes. Further studies should investigate the longer-term role of vaping on future smoking habits with the use of causal inference methods.	Please see table 1, answer 5.
276	Gibson Erica, TES T COMMENT, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	Apologies for this - we are making a test submission to check on attachments and also to ascertain if we can make more than one submission on the same subject. Thank you	There is no comment in this contribution.
277	Gallus Silvano, Italy	6.6 Role in the initiation of	Page 62 line 45 (and section 6.7, and abstract lines 42-47): I absolutely agree with the SCHEER Report suggesting that	Thank you for your comment.

	tuto di Ricerche Farmacologiche Mario Negri IRCCS, Italy	smoking (particularly focusing on young people)	electronic cigarettes represent a gateway towards smoking initiation for young people. This is true not only for young people. In fact, a series of representative cross-sectional studies annually conducted in Italy between 2014 and 2018 showed that among all Italians reporting to be ever electronic cigarette users, those (re)starting smoking after using e-cigarettes outnumber those who stop smoking after using e-cigarettes (Liu X, Lugo A, Davoli E, Gorini G, Pacifici R, Fernández E, Gallus S. Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco? Tob Control. 2020 Mar;29:148-152).	
278	No agreement to disclose personal data	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>THERE IS NO EVIDENCE THAT E-CIGARETTES ARE SERVING AS A GATEWAY TO CIGARETTE SMOKING AMONGST NEVER-SMOKERS</p> <p>Scientific and real-world evidence shows smoking rates across the EU are at an all-time low, and demonstrates e-cigarettes are a gateway away from tobacco smoking. We provide SCHEER with a non-exhaustive list of studies whose thorough analysis was omitted from the Opinion. In the UK, the largest ever analysis of data from 60,000 11-16-year-olds found no evidence that e-cigarette use is leading to young people into smoking. Among young people who have never smoked, regular use of e-cigarettes was negligible – between 0.1% and 0.5% across the five surveys assessed[1]. In Greece, e-cigarette use has been shown to be largely confined to current or former smokers, with current regular use by never smokers “extremely rare” (< 0.2%)[2]. Another study showed the vast majority of Greek daily e-cigarette users were smokers (<98%) before initiating e-cigarette use with the authors noting “E-cigarette use by never smokers is rare and none of them subsequently initiate smoking”[3]. Current and daily e-cigarette use in Greece is also strongly associated with recent smoking cessation[4]. In France, a study commissioned by Public Health France found that from 2010-2017, 700,000 smokers used e-cigarettes to quit smoking and less than 1% of vapers were never smokers [5]. Another study found no evidence of an increased risk of transitioning to daily smoking at age 17 among French ever-smokers who also experimented with e-cigarettes[6]. In the US, an analysis of first experimentation with different types of tobacco products (including e-cigarettes) among 40,000 US adolescents found that <1% adolescents who tried e-cigarettes then became established smokers, with the association of</p>	Please see table 1, answer 5.

subsequent e-cigarette use stronger for adolescents initiating with combustible cigarettes than the association of subsequent cigarette smoking for e-cigarette initiators [7]. An analysis of the US NYTS dataset showed that among tobacco naïve adolescents, 0.4% regularly used e-cigarettes on 20+ days[8].

Page 62 Line 22: E-LIQUID FLAVOURS ARE AN IMPORTANT FACTOR IN ADULT SMOKERS' TRANSITIONING AWAY FROM TOBACCO CIGARETTES

Substantial research shows flavours play a critical role in attracting - and retaining – adult smokers into the e-cigarettes category, directly contributing to tobacco harm reduction and declining smoking rates. Flavours ensure adult smokers find e-cigarettes palatable and therefore easier to transition to. Regular use of multiple e-liquid flavours has been shown to be associated with significantly higher odds of having quit smoking [9] and flavoured e-cigarette use is associated with higher rates of smoking cessation[10]. Daily e-cigarette use of flavoured products is also associated with higher odds of being a former smoker[11]. Data from the US shows that non-tobacco flavours are no more associated with youth smoking initiation than tobacco flavours, but are associated with increased adult smoking cessation amongst adults, with those who began e-cigarette use with non-tobacco flavours more likely to quit smoking than those who use tobacco flavours[12]. Consistent with this, US adult smokers tend to initiate e-cigarette use with tobacco-flavours, but then transition to exclusive or predominant use of non-tobacco flavoured products, particularly fruit, sweet and dessert flavours[13]. Moreover, US adult smokers who transition to non-tobacco flavoured e-cigarettes (or multiple non-tobacco/menthol flavours) are 2.5-3 times more likely to have quit or reduced smoking in the past year compared to non-e-cigarette users[14].

Please see Table 1, answer 7.



6.6_Role_in_the_initiation_of_smoking__par

279	Chaplia Maria,Con sumer	6.6 Role in the initiation of smoking	PAGE 64, Line 34 - Flavours play a key role in helping smokers quit. Legislation on vaping flavours must take this fact into account. Survey results from the longitudinal survey study from Yale School	Please see Table 1, answers 1 and 7.
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Choice Center, United States (particularly focusing on young people)

of Public Health found that “relative to vaping tobacco flavours, vaping non-tobacco-flavoured e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation”.

A study from Yale School of Public Health discovered that fruity and sweet flavours are over twice as likely to help smokers quit cigarettes.

Page 65, lines 55-57, Page 66, Lines 1-2
We agree with the report that age limits and buying restrictions for adolescents are necessary. Minors should not be allowed to purchase vaping products, and so it is important to create and sustain the conditions under which there is no incentive for them to look for e-cigarettes elsewhere. Vaping regulations should be smart and ensure the necessary age restrictions are put in place. Reducing black market activities and illicit trade are vital to reducing underage vaping. However, the recommendation to ban flavours will create more harm than doing any good whatsoever. Banning flavours would have a profoundly negative effect on society, pushing smokers back to cigarettes or to the black market, which has happened in, for example, some states in the United States who have implemented such bans, as shown in this report.

Gateway hypothesis: see comments above.
Page 67, LINES 11-24: Renormalization hypothesis: the statement seems to overlook the true essence of addiction. In the average dosage in vaping or smoking, nicotine mimics some of the effects of an endogenous substance (acetylcholine) and thereby activates nerve cells in the brain and in the autonomic nervous system. Professor Bernd Mayer (toxicologist at the University of Graz) explains that “the effect as a nerve poison, the blockage of the function of nerve cells, only occurs in the event of a massive overdose, which is not achieved with inhalation. The addiction to smokers is based on a combination of nicotine and other ingredients of tobacco smoke together with conditioned behaviour [the so-called ‘smoking ritual’].” In the absence of tobacco smoke, the potential for addiction to nicotine is very low, so that most vapers feel much less addictive pressure than smokers.

Please see table 1 answer 5

Moreover, The 2018 U.S. National Academies of Sciences, Engineering, and Medicine Report found that the smoking rate has decreased overall more rapidly since vaping became more prominent in the United States. The researchers concluded: “The inverse relationship between vaping and smoking was robust across different data sets for both youth and young adults and for current and more established smoking.

Ref: Levy (2019). Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check Beard (2019). Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017.

Friedman (2020). Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation.

Leaflet: Clement Why Vape Flavours Matter

280 O’Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy

6.6 Role in the initiation of smoking (particularly focusing on young people)

P67 Gateway section A study in France (Chyderiotis et al., 2020) of 17,862 17 year old ever-smokers from the Department of National Civil Service and Youth 2017 Escapad Survey (government required compulsory participation) found that youth who ever-used ENDS were less likely to be daily cigarette users (RR=0.62, CI 0.60-0.64) than ever-smokers who had never tried ENDS. Youth who tried ENDS first before ever-smoking were less likely to be daily cigarette users (RR= .76, CI 0.66 – 0.89). A study (Shahab et al., 2020) of 38,620 youth from the US National Youth Tobacco Surveys 2014-2017 found that youth who tried ENDS before cigarettes were less likely to be past 30 day cigarette users (OR 0.15, CI 0.12-0.18) or established cigarette smokers (OR 0.04, CI 0.03-0.07). Seyla et al. (2018) followed the smoking trajectories of 1007 Chicago US 9th and 10th grade students (79.7% retention, n=299 any past-30-day ENDS use) for eight years. “E-cigarette use did not predict later conventional smoking and nicotine dependence” (p. 330). Researchers surveying 1435 French 15-16 year olds conclude that ENDS use “in non-smoking adolescents does not appear to be a major mode of entry into smoking or nicotine addiction” (Denis-Vatant et al., 2019, p.3). A review on youth ENDS use concludes there is no strong evidence supporting the gateway hypothesis (Siddiqui et al., 2019, see also Cahn et al., 2020). Shahab et al. (2020), Chyderiotis et al. (2020),

Please see Table 1, answer 5.

and Seyla et al. (2018) state that their findings contradict the gateway hypothesis. P69 L45 A “resurgence of cigarette smoking” indicating a renormalization of smoking has not occurred. Based on WHO data for 2016 and 2018 on cigarette smoking prevalence for the population 15 years old and older, 24 of 27 EU member states experienced declines in the prevalence of cigarette use. Seven countries had cigarette prevalence declines of 6% or better and three countries had declines over 10% during the 2-year period. See WHO Cigarette Data file. P64L45-P66L2 A longitudinal cohort study (Friedman & Xu, 2020) analyzed data from waves 1 to 4 of the Population Assessment of Tobacco and Health Study (2013 to 2018). For youth (n=7311) use of nontobacco flavors was no more associated with youth smoking initiation than use of tobacco-flavors (AOR 0.66; CI 0.16-2.76). For adults under 55 years old (n=5984) use of non-tobacco flavours increased smoking cessation compared to tobacco flavors (2.28; CI 1.04-5.01). This finding is corroborated by longitudinal data from the Population Assessment of Smoking and Health surveys (PATH) as flavoured ENDS substantially improved quit rates among US adults using ENDS for smoking cessation, RRR 1.75 (CI 1.18-2.60) for past year quitters and RRR 2.83 (CI 1.69-4.73) for 1+ year cessation (Glasser et al., 2020). Flavors are not the primary driver of youth experimentation with ENDS. In the 2019 US National Youth Tobacco Survey (Wang et al., 2019) flavors ranked third in the reasons for use (22.3%), with curiosity the major reason for trying ENDS (56.1%), followed by use by family or peers (23.9%). Interestingly, the ability to use ENDS for playing tricks (21.2%) was just as common a reason as flavors for trying ENDS. In a small survey of adult ENDS users in the Netherlands 24.6% endorsed cloud chasing tricks as an attractive feature of ENDS (Romijnders et al., 2019). A 2018 survey of French youth (age 15-16, N=1435) states that curiosity was the most common reason for trying ENDS, followed by flavours (Denis-Vatant et al., 2019, data not reported). For French young adults (19-22 years old) a 2016 survey (N=2720) found that 77.4% tried ENDS out of curiosity, 63.5% because someone offered it to them, and 24.6% because of flavors (Kinouani et al., 2017).

Ref:

Cahn, Z., Drope, J., Douglas, C. E., Henson, R., Berg, C. J., Ashley, D. L., & Eriksen, M. P. (2020). Applying the Population Health Standard to the Regulation of Electronic Nicotine Delivery Systems. *Nicotine & Tobacco Research*. Accepted Manuscript

Friedman, A. S., & Xu, S. (2020). Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. *JAMA Network Open*, 3(6), e203826-e203826.

Glasser, A., Vojjala, M., Cantrell, J., Levy, D. T., Giovenco, D. P., Abrams, D., & Niaura, R. (2020). Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine & Tobacco Research*. Accepted manuscript published 17 September 2020

Selya, A. S., Rose, J. S., Dierker, L., Hedeker, D., & Mermelstein, R. J. (2018). Evaluating the mutual pathways among electronic cigarette use, conventional smoking and nicotine dependence. *Addiction*, 113(2), 325-333. doi:10.1111/add.14013

Siddiqui, F., Mishu, M., Marshall, A. M., & Siddiqi, K. (2019). E-cigarette use and subsequent smoking in adolescents and young adults: a perspective. *Expert Review of Respiratory Medicine*, 13(5), 403-405, DOI: 10.1080/17476348.2019.1589371

Wang, T. W., Gentzke, A. S., Creamer, M. R., Cullen, K. A., Holder-Hayes, E., Sawdey, M. D., ... & Jamal, A. (2019). Tobacco product use and associated factors among middle and high school students—United States, 2019. *MMWR Surveillance Summaries*, 68(12), 1.

Table. WHO Cigarette Smoking Prevalence Data.

281	Wyszynski-Szulc Agnieszka, Philip Morris Products S.A., Switzerland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>P. 62 l. 48-54 We suggest including the most recent prevalence data on e-cigarettes, such as Public Health England (McNeill 2020) and ASH UK (2020). This data shows that youth prevalence remains low in the UK and that “current vaping is mainly concentrated in young people who have experience smoking. Less than 1% of young people who have never smoked are current vapers”. We also recommend adding the recent data from the US showing a decline in youth cigarette use in that country (Wang 2020). Furthermore, we suggest the following changes:</p> <p>P. 63 l. 21: Add the sentence: “However, available data from the UK, where e-cigarettes’ use is widespread, show that regular use among youth is low, while the latest data set from the U.S. shows a declining trend within this population.”</p> <p>P. 64 l. 35 – P. 66 l. 2 We suggest adding the studies that show the role of flavours in</p>
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See Table 1, Answer 11.

helping smokers switch to e-cigarettes.

While it is relevant to analyze whether flavours can make e-cigarettes more attractive to youth, it is also relevant to analyze evidence on their influence in helping smokers quit smoking by switch to e-cigarettes. Several studies conclude that non-tobacco flavours and non-menthol flavours, especially fruit flavours, facilitate the switching of smokers compared to traditional tobacco and menthol flavours including Romijnders (2019), Gravelly (2020), Friedman (2020), Havermans (2019), Du (2020) and Russel (2018). These were not included in the SCHEER's Opinion.

P. 66 l. 2
We suggest adding Public Health England's advice that "a ban on flavoured liquids could have the adverse effects and unintended consequences for smokers using vaping products to quit. It should only be considered with caution." (McNeill 2020).

P. 66 l. 3
We suggest to add the relevant findings from Romijnders (2019) and Leventhal (2019) on the need for a balanced approach to regulation of flavours.

P. 67 l. 11 – P. 70 l. 15
We suggest that the SCHEER reconsiders the weight afforded to the available evidence as the SCHEER's Opinion fails to reference several studies from EU countries that dismiss the gateway hypothesis. It is also important to mention that the concept of "gateway theory" is being largely questioned by public health experts. See for example McNeill (2015) and Etter (2018).

P. 68 l. 53-55
We suggest to include the following studies: data from Chyderiotis (2020) show that adolescents in France who have tried e-cigarettes are less likely to later transition to daily smoking than those who had not; data from Italy (Gorini 2020) indicate that e-cigarettes do not seem to have determined an increase in tobacco smoking between 2010 and 2018; and a survey from Greece (Soteriades 2020) concluding that "it seems that e-cigarette use may contribute

See Table 1, Answer 7.

On the other hand, 32% expresses interest in trying a flavour, which is concerning.

Please see Table 1, Answer 7.

Please see Table 1, answers 5 and 8.

Please see table 1 answer 1

			to a net reduction in the use of combustible tobacco products among adolescent students”.		
			P. 70 l. 15 In the view of the above referenced studies, we suggest to add the following: “At the same time there is growing evidence that flavours may contribute to help smokers quit or switch to e-cigarettes.”		
282	Serafimov Lubomir, Bulgarian Vape Association of Manufacturers, Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E-liquid, Bulgaria	6.6 Role in the initiation of smoking (particularly focusing on young people)	Page 52	lines: 13-49	
			SCHEER draws a confident conclusion that e-cigarettes are a gateway to smoking or the initiation of smoking, declaring that the evidence of a gateway effect is “strong”. No other authorities share this confidence. Smoking and vaping are very similar behaviors (albeit with radically different risks) and therefore the factors that cause people to smoke are likely also to cause them to vape. However, the SCHEER opinion omits the important role of e-liquid flavors in switching adult smokers to less harmful vaping products, and instead focuses only on the enhanced attractiveness for youth and potential gateway effect which is not supported by available evidence from the EU. The gateway concept itself is barely defined by SCHEER – i.e. what is the relevant exposure and the outcome of concern, and how would you test that the exposure caused the outcome? Whether vaping or smoking came first in a period of teenage experimentation is of little interest and it would never be possible to show that one caused the other. In its 2015 report, (E-cigarettes: an evidence update) Public Health England’s expert reviewers showed that there was little of substance to gateway claims made at the time and advised: “We strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field.” A more useful definition of a gateway effect would be if a substantial number of young people were reaching, say, age 20 as regular smokers because of a period of vaping in their teenage years. This would be a genuinely concerning outcome. There is no evidence to support this effect. Not only that, it is impossible to tell what these young people would have done in the absence of e-		Please see Table 1, answer 5.

cigarettes. To the extent that there is evidence, it suggests the more frequent adolescent users of e-cigarettes are those who were previously smokers or would-be smokers – for these teenage users, e-cigarette use may be beneficial, if not now, in the future as a diversion from smoking. RIVM publication (Romijnders 2019) demonstrates that among participants who reported to never have smoked and never have used an e-cigarette the majority (68%) of the participants were not interested in trying a flavored e-cigarette. SCHEER points out that e-liquid flavours do not cause known health problems (correct), but may “enhance attractiveness”. Indeed, flavours are integral to the product appeal of e-cigarettes. However, this expression “enhance attractiveness” is used throughout the opinion as though attractiveness is a bad thing and therefore that unattractive products would be better. On the contrary, in a situation where 26% of European Union adults are smoking and approximately 700,000 dying as a result annually, the availability of an attractive low-risk alternative provides options for smokers to switch and greatly reduce their personal risk – on their own initiative and at their own expense because they find the idea attractive.

If European policymakers read this opinion as advice to reduce the attractiveness of e-cigarettes, then they will be introducing regulatory protections to the cigarette trade and, in relative terms, improving the attractiveness of the remaining as a smoker – with certain harm to health. source: <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>
<https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>

Ref.: Jarvis (2020). Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA?

Please see Table 1, answer 1.

On the other hand, 32% expresses interest in trying a flavour, which is concerning.

283	Wacław Michalina, Prawo dla Ludzi (Law for	6.6 Role in the initiation of smoking (particularly focusing on young people)	Another question raised by the SHEER report concerns the presentation of e-cigarettes as a "gateway to addiction". The report categorically states that due to the availability of flavored liquids, vaping causes more and more young people to smoke cigarettes. Of course, there is a slight link between e-cigarettes and the start of smoking by young people. However, according to research: Chan	Please see Table 1, answer 5.
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	People), Poland		GCK et al. 2020, Gateway or common liability? A systematic review and meta - analysis of studies of adolescent e - cigarette use and future smoking initiation. "The evidence is limited by publication bias, high degree of sample discrepancy and inadequate alignment with potential confounders."
284	Sweeney Damian, European Tobacco Harm Reduction Advocates, Ireland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Flavours, pages 64 (lines 35 - 57) & 65 (lines 1 - 57)</p> <p>The report misses the point of flavours in e-liquid. These are consumer products and in order for adult smokers to want to use them they have to be appealing. Attractive flavours are critical factors in the effectiveness of e-cigarettes for smoking cessation, also why Nicotine Replacement Therapy products come in a range of fruity and mint/menthol flavours. As the Royal College of Physicians pointed out on page 187 of their report, Nicotine Without Smoke (2016), "if a risk-averse approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking."</p> <p>The SCHEER Opinion regarding flavours disregards the importance of flavours for adults, who make up the majority of e-cigarette users. The report instead focuses on youth use which has already been demonstrated to be rare among never smokers, "frequent use and signs of e-cigarette dependence remained rare in students who had only ever used e-cigarettes and never any other tobacco product" (Jarvis et al 2020).</p> <p>Wang et al found that the main reason for youth experimentation with e-cigarettes was curiosity (55.3%), and flavours were a distant third as a reason for trying e-cigarettes (22.4%). The importance of flavours to adults has been demonstrated in numerous studies. Farsalinos et al (2018) concluded that fruit and dessert/pastry/bakery flavours, were the most prevalent choices of adults who had completely switched from smoking to vaping. Disassociation with the taste of tobacco, as well as enjoyment of the product being used, are very important factors for adult smokers switching to e-cigarettes.</p> <p>Havermans et al (2019) is cited in the section dealing with That is not a finding of Havermans et al., so no change needed.</p>

categories of flavours available in the Netherland (page 25 lines 7-14), but the most important findings of the study seem to have been omitted. Adults who have completely switched from smoking to e-cigarettes have often initiated e-cigarette use with fruity flavours rather than tobacco flavours, or switched from tobacco to non-tobacco e-liquid flavours over time.

Friedman and Xu (2020) examined the association of flavoured e-cigarettes with subsequent smoking cessation and found that adults who vaped non-tobacco flavours were more likely to quit smoking than those who vaped tobacco flavours.

Please see Table 1, answer 7.

Yang et al (2020) assessed the impacts of a flavour ban in California and they found that “comprehensive local flavor bans, by themselves, cannot sharply reduce the availability or use of flavored tobacco products among residents. Nevertheless, local bans can still significantly reduce overall e-cigarette use and cigar smoking but may increase cigarette smoking.”

Product appeal is a key element of the efficacy of e-cigarettes in transitioning adult smokers away from combustible tobacco. A critical part of that is having a range of flavours that can be tailored to each individual needs and tastes. Restricting or banning the flavours which adults use to remain smoke free will have the unintended consequence of prolong smoking, thereby increasing the harms from smoking related diseases.

Please see Table 1, answer 1.

References:

- Friedman, Qing(2020) Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation JAMA Network Open.2020; 3(6):e203826. doi:10.1001/jamanetworkopen.2020.3826 R
- Jarvis (2020). Epidemic of youth nicotine addiction. What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? <https://doi.org/10.32388/745076.5>
- Royal College of Physicians 2016. Nicotine without smoke, Page 187.
- Farsalinos (2018). Patterns of flavored e-cigarette use among adults vapers in the United States an internet survey
- Yang (2020). The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. <https://doi.org/10.1016/j.abrep.2020.100273>
- Morbidity and Mortality Weekly Report, December 2019. Tobacco Product Use and Associated Factors Among Middle and High School Students United States 2019.

285	Sweeney Damian, European Tobacco Harm Reduction Advocates, Ireland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Pages 62, 63, and 64 SCHEER acknowledges in this section that most of the included studies were carried out in the USA, and acknowledges that USA data may not reflect the situation in the EU (lines 50-52). SCHEER are comparing apples and oranges, as there are significant differences in e-cigarette use between the US and the EU. The different regulatory systems and variance in product availability render the US data irrelevant in the EU context. USA youth usage data includes use of products not available in the EU: high nicotine pods and cannabis products. Past 30-day use, or experimentation, is the main driver of increased vaping prevalence in the USA, which is less likely to lead to smoking than regular use. European smoking prevalence data is not considered in the report, however, to prove the “gateway effect” in youth, smoking prevalence would need to be shown to have increased.</p>	Please see Table 1, answer 8.
			<p>Data from the CDC found that “From 2014 to 2018, the percentage of adults aged 18–24 years who currently smoked cigarettes decreased from 16.7% to 7.8%. The percentage of adults in this age group who currently used electronic cigarettes increased from 5.1% to 7.6%” (Survey and States, 2019). A forensic examination of the National Youth Tobacco Survey by Jarvis et al (2020) found that “frequent use and signs of e-cigarette dependence remained rare in students who had only ever used e-cigarettes and never any other tobacco product”. Highlighting once again the falling smoking prevalence among US youth, Levy et al (2019) conclude that “While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance.” The Opinion acknowledges there was a decline in youth smoking during the same timeframe as there was an increase in youth e-cigarette use in the USA (page 17 lines 30-32).</p>	
			<p>The EU has a comprehensive regulatory regime for e-cigarettes, the TPD, so it is necessary to examine data from Europe to assess e-cigarette use within Europe. Here are three examples of relevant European studies, with their findings: The German Cancer Research Centre report (DKFZ, 2020) found that: “Even if</p>	

numerous studies suggest a connection between e-cigarette consumption and smoking, this has apparently only had little and different effects at the population level”. A French study by Chyderiotis et al (2020) concluded that “Among ever-smokers, adolescents who declared having ever used e-cigarettes were less likely than those who did not to transition to daily smoking at 17.” And, in the UK, Bauld et al (2017) found that “most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low”

Public Health England has cautioned against using gateway terminology: “We strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field.” (McNeill et al., 2015 page 38). Population level data from across Europe shows a continual decline in smoking rates across all ages group.

Ref.uploaded:
 Chyderiotis (2020). Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France?
 Jarvis (2020). Epidemic of youth nicotine addiction. What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? <https://doi.org/10.32388/745076.5>
 Levy (2019). Examining the relationship of vaping to smoking initiation among US youth and young adults a reality check
 Morbidity and Mortality Weekly Report, page 870, October 4, 2019
 McNeill et al. (2015) E-cigarettes: an evidence update. A report commissioned by Public Health England.
 Bauld (2017). Young People s Use of E-Cigarettes across the United Kingdom Findings from Five Surveys 2015-2017

286 Vape Business Ireland,Irel and (particularly focusing on young people)
 6.6 Role in the initiation of smoking

There needs to be greater objectivity in the debate regarding the uptake of vaping among young people. The picture varies across the globe and the wider regulatory environment is a critical context that needs to be borne in mind. The literature that is cited in the SCHEER Preliminary Opinion relates to the situation in the USA. However, the regulations that control the sale of vaping products in the USA are quite different to the regulatory environment in, Europe. The broader policy environment and regulations covering the sale, presentation and purchase of these products needs to be considered.

Please see Table 1, answer 8.

NICOTINE

The report focuses on nicotine concentration in vaping products as a concern for the TPD. Nicotine levels in vaping products are already set at a level that means they can't compete with cigarettes despite the TPD specifying that nicotine levels be allowed at levels sufficient to allow vaping products to deliver nicotine at a comparable level as a cigarette.

Please see Table 1, answer 9.

Vaping products in general contain far less nicotine than a cigarette and are far less effective at delivering it. Several studies (e.g. Hajek 2015) show that TPD compliant vaping products do not deliver nicotine at the same rate as cigarettes, even at levels much higher than in EU vaping products.

FLAVOURS

Flavours play an important role in keeping smokers smoke-free. Studies show that when smokers start vaping, they often instinctively start with a tobacco flavour. But long-term studies show that flavour preference changes over time. A landmark study (Hajek 2015) showed that when smokers initially given tobacco-flavour e-liquids could choose their own flavour, approximately 60 per cent chose non-tobacco or menthol flavours. A recent longitudinal study (Ping Du et al 2020) showed that at the beginning of the study, tobacco and fruit were the most preferred flavours followed by mint/menthol. Preference for tobacco flavour decreased significantly over time as preference for sweet flavours increased significantly. About 40 per cent of participants maintained their initial flavour preferences. All age groups showed significant migration away from tobacco flavour towards sweet flavours. Preference for tobacco flavour also decreased nearly two-fold among groups 60 years or younger. About 50 per cent of participants in this study reported they would "find a way to buy my preferred flavour" or "add flavouring agents myself" if their preferred flavour were banned. Approximately 10 per cent reported they would return to smoking traditional tobacco cigarettes if all non-tobacco flavours were banned. Restrictions on flavours would likely cause harm to vapers and adult smokers who are yet to make the switch by reducing the less harmful alternatives available to them. The results of these and other studies suggest that rather than attracting people to vaping,

Please see Table 1, answer 7.

flavours play an important in keeping smokers who have chosen to smoke away from cigarettes.

GATEWAY

The SCHEER report conclusion that vaping is a gateway to smoking is not evidenced-based and is a misleading statement which, if adopted as a policy, would cause untold damage to the public health of smokers across Europe. Bauld et al. 2017 reported that ‘surveys across the UK show a consistent pattern: most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low.’ A rise of vaping in the UK and US has been accompanied by rapid falls in adult smoking, and there is no compelling evidence that vaping causes smoking (Kozlowski et al 2017).

Please see Table 1, answer 5.

Ref:

Du 2020 Changes in Flavor Preference in a Cohort of Long-term Electronic Cigarette Users

McNeill (2015). E-cigarettes: an evidence update A report commissioned by Public Health England

McNeill (2015). Underpinning evidence for the estimate that e-cigarette use is around 95% safer than smoking: authors’ note

287 Compernelle Thomas, British American Tobacco, Belgium
6.6 Role in the initiation of smoking (particularly focusing on young people)

The Sheer Opinion concludes there is strong evidence that e-cigarettes are a gateway to smoking for young people.

Please see Table 1, answer 5.

Efforts to assess whether e-cigarette use causes cigarette smoking must consider “common liability,” taking into account that predisposing factors of e-cigarette use are common to those of cigarette smoking. The common liability model, where inclination towards risk-taking and psychosocial processes can be factors, provides a parsimonious explanation of substance use co-occurrence (1-3).

SCHEER’s Opinion proposed two hypotheses (gateway and renormalization), neither of which take into consideration the common liability model or providing evidence on causality among the studies synthesized. The systematic reviews in the Opinion do not support the gateway hypothesis. Glasser et al. (2019) notes that causal inferences are not supported by the evidence, and that youth

using both e-cigarettes and cigarettes share a number of confounding factors that increase susceptibility to use either product (1). In particular, willingness to take risks, and perception of relative cigarette and e-cigarette risks and/or benefits all differentially influence cigarette smoking initiation (4). One cited study presents the inadequate control of confounding factors in the body of evidence and consequently challenges the existence of a gateway effect (5). The Opinion fails to account for various definitions of initiation of cigarette smoking among the studies. In most cases, definitions of initiation are more consistent with experimentation (e.g., “ever use”) than true initiation (1, 6).

Independent organisations have criticised ‘gateway’ arguments and concluded that there is no reliable evidence of a gateway effect (7-9). Data from ASH UK finds that youth smoking rates are at an all-time low and youth use of e-cigarettes UK is rare and largely confined to those that already smoke cigarettes (10). Recent US National Youth Tobacco Survey data does not support a rise in youth nicotine dependence from e-cigarettes or a reversal in decreasing youth cigarette smoking prevalence (11).

The Opinion suggests that e-cigarette use plays a role in the initiation of smoking by emphasizing prevalence of e-cigarette awareness and use, preferences for flavours, levels of nicotine, and motivations for use. The Opinion fails to contextualize the findings and does not consider alternative hypotheses. An equally valid hypothesis is that the increase in e-cigarette use coupled with the recent and rapid decline of cigarette use among youth could mean that youth who are predisposed to smoke cigarettes are being redirected to a potentially less harmful product. A recent study showed that in the US, adolescents who (first) use e-cigarettes are less likely use cigarettes in future (12.) A 2020 study using survey data from the US Population Assessment of Tobacco and Health (PATH) Study showed that flavoured e-cigarettes were not associated with greater youth smoking initiation but with greater adult smoking cessation (13). Public health experts have recognised the important role that flavours have in increasing the potential for vapour products to act as a satisfactory alternative to cigarette smoking, and an important factor for smokers who are looking for

See Table 1, answer 7.

alternatives to cigarettes (14-15). Flavours and efficient nicotine delivery play an important role in improving the overall appeal for less harmful nicotine products such as e-cigarettes, when compared to cigarettes (15-17).

The SCHEER Opinion fails to provide evidence that supports a direct association between e-cigarette use and resulting cigarette smoking or even define how the gateway theory can validly be tested and we respectfully request SCHEER to readdress their conclusion.



ref-287.docx

Please see Table 1, answer 5.

288	Sweeney Damian, European Tobacco Harm Reduction Advocates, Ireland	6.6 Role in the initiation of smoking (particularly focusing on young people)	Page 70, lines 12 to 15 SCHEER concludes that there is strong evidence that e-cigarettes are a gateway to smoking but without examining smoking prevalence data it is not possible to reach this conclusion. Associations between e-cigarette use and smoking are treated as causal in the report when a more realistic explanation might be that both behaviours share a common liability. Chan et al (2020) carried out an extensive systematic review and meta-analyses, examining association between youth e-cigarette use and future smoking. They found that “the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders.” Lee, Coombs and Afolalu, (2019) summed up the gateway theory with regards to e-cigarette use: “if a true gateway effect were to exist, it would probably have little effect on smoking prevalence. No available evidence exists that increasing e-cigarette use has slowed the decline in smoking prevalence; indeed, the decline appears to have accelerated.” It is very possible that e-cigarettes are lessening youth initiation of smoking, but the report fails to examine this. . Ref: Lee PN, Coombs KJ, Afolalu EF. (2018). Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review. F1000Res. 2018;7:1915. Chan (no year) Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation
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Please see Table 1, answer 5.

289	Arffman Päivi, Vapers Finland, Finland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>6.6 Role in the initiation of smoking (particularly focusing on young people) (page 62, line 45 - page 64, line 27). All sections on the use of e-cigarettes among young people lack information on the regularity of use among young people who have never smoked, which is essential information when evaluating both the health risks of e-cigarette use and its potential addictiveness. Regular use of e-cigarettes by never-smoking youth is very rare. In the United States, for example, among never-smoking young people regular use of e-cigarettes (≥ 20 days/month) was 0,4% in 2018, Great Britain 0,1% in 2019 (weekly), Finland 0,4% in 2015 (weekly).</p> <p>Ref: Kinnunen (2016). Changes in Electronic Cigarette Use from 2013 to 2015 and Reasons for Use among Finnish Adolescents ASH 2019. Use of e-cigarettes among young people in Great Britain Glasser (2020). Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey</p>	See Table 1, answer 5.
290	Accorinti Sandro, Italy	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>6.6 Role in the initiation of smoking (particularly focusing on young people) 64 line 34 - 66 line 2</p> <p>Comment: European Heart Network recommends flavours should be prohibited (line 55)</p> <p>Royal College of Physicians: “However, if [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.”</p> <p>From section 12.10 page 187</p> <p>Bans lead to more smoking: “local bans can still significantly reduce overall e-cigarette use and cigar smoking but may increase cigarette smoking.”</p> <p>SCHEER disregards benefits to adults</p> <p>- Importance of flavours to adults shown in many studies, including Havermans study (frequently quoted in SCHEER): “Furthermore, adults who completely substituted the use of conventional cigarettes by e-cigarettes have often initiated e-cigarette use with fruity flavours rather than tobacco flavours, or switched from tobacco to non-tobacco e-liquid flavours over time”</p>	Please see table 1, answers 1 and 7.

291	Michel Nicolas,As sociation Romande des Profession nels de la Vape,Swit zerland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Gateway Page 68</p> <p>35 On the antipode however are a number of studies that indicate that exposure to electronic 36 cigarette use may not be directly related to smoking uptake among youth. A time trend 37 analyses on national representative data on electronic cigarette and tobacco use in the US 38 by Levy et al. (2019) noted a decline in past 30-day smoking prevalence between 2014- 39 2017, which coincides with the timeframe of electronic cigarette proliferation in the US, 40 however the authors noted that while there has been a decrease in smoking rates during 41 the past years in the US, this could also be attributable to the influence of other tobacco 42 control interventions. Whoever does not know history is condemned to relive it. In 1992, snus was banned from sale throughout Europe, except in Sweden. At that time longitudinal studies were used in the same way to justify the theory of a gateway effect from snus to smoked tobacco. 28 years later Sweden has the lowest smoking rate in Europe, and also the lowest lung cancer rate in Europe, but opponents of snus continue to invoke the gateway effect to justify its ban. By what mechanism a high prevalence of snus in Sweden coupled with a gateway effect can lead to the lowest smoking rate in Europe, the question seems relevant. In the USA, France and England, a drop in smoking prevalence has been observed in parallel with the arrival of the vape. We can therefore draw a parallel between the so-called gateway effect of snus and vape. Are the analysis biases the same? Have correlations been unduly considered as evidence of causality? Potential confounding factors, inherent in the comparison of two products that are too close to be able to dissociate the correlation of risk behaviours from true causality, may explain an analytical error. The gateway theory is not compatible with either (1) the decrease in smoking prevalence observed in adolescents in countries where vaping increased or (2) an increase in smoking among teenagers after age restrictions were imposed on e-cigarette purchases. https://pubmed.ncbi.nlm.nih.gov/28786147/ ST use has played virtually no role in smoking initiation among White men and boys, the demographic groups among which ST use is most prevalent. There is evidence that, compared with cigarette</p>	Please see Table 1, answers 5. 6, 7, 8.
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initiators, ST initiators are significantly less likely to smoke. This suggests that ST may play a protective role. <https://pubmed.ncbi.nlm.nih.gov/20335282/>

The report also asserted that the common liability theory is a plausible explanation for the association between vaping and smoking (i.e. both are determined by the same risk factors) <https://www.tandfonline.com/doi/pdf/10.1080/17476348.2018.1453809>

292	Michel Nicolas, Association Romande des Professionnels de la Vape, Switzerland	6.6 Role in the initiation of smoking (particularly focusing on young people)	Gateway 13 There is also strong evidence that nicotine is implicated in the development of addiction.	2	Page 70	Please see table 1 answers 5 and 7
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This part of the report is not supported by the figures stated:
 Page 69
 19 Previous secondary data set analyses using the 2012, 2014 and 2017 Eurobarometer 20 datasets had indicated that ever use of an electronic cigarette in the EU Member states 21 increased from 7.2% (95% CI 6.7 - 7.7) in 2012, to 11.6% (95% CI 10.9 - 12.3) in 2014 to 22 14.6% (95% CI 13.9–15.3) in 2017. Across the whole of the EU 1.8% of the adult 23 population (95% CI 1.5 to 2.1) were current regular electronic cigarette users in 2017,24 compared with 1.5% (1.2–1.8) in 2014 (Filippidis et al., 2018; Laverly et al., 2018) According to the Inpes Youth Health Barometer 2010,« chez les jeunes de 20/25 ans ayant fumé leur première cigarette avant 14 ans, 66 % fument quotidiennement et 51 % fument au moins 10 cigarettes par jour. Alors que pour ceux ayant fumé leur première cigarette entre 14 et 17 ans, c'est 52 % qui fument quotidiennement et 30 % qui fument au moins 10 cigarettes par jour »
 If vaping was as addictive as tobacco, around half of the people who experimented with vaping in 2014 should be addicted to it in 2017. However, we went from 11.6% of experimentation in 2014 to 1.8% of use in 2017. A majority of them are smokers or ex-smokers for whom the cause of nicotine addiction is tobacco and not vaping. This report therefore claims that vaping is addictive but shows the opposite in the figures.

We know that nicotine is addictive, but also that its addictive potential depends on the mode of absorption. Eggplants and potatoes, which contain nicotine, are not know to be addictives.

Patches are not known to be addictive, nicotine gum is very little. Here again, the SCHEER report mentions evidence without quantifying it and qualities evidences as "strong" even though it is not correlated with demographic data.

This is to our knowledge the first report of addiction to nicotine gum in never users of tobacco. However, this phenomenon is rare <https://bmcpublichealth.biomedcentral.com/articles/10.1186/1471-2458-7-159>

Due to dissonance between studies, we might be tempted to look into the mechanisms of the gateway effect. Does the gateway effect concern young people who have just experimented vaping or only those who have become addicted to nicotine? Why will young people who have experimented with vaping choose to smoke or not? Compared to the vape => tobacco gateway effect, what is the tobacco => vape gateway effect? Are there any qualitative studies on the subject? Une porte d'entrée vers le tabagisme ? Aucun élément dans les témoignages que nous avons recueillis ne peut laisser penser que la cigarette électronique pourrait être une « porte d'entrée vers le tabac » pour les plus jeunes utilisateurs. <https://www.cairn.info/revue-sante-publique-2017-6-page-793.htm>

293	Ikonomidis ,MD,PhD, FESC Ignatios , National and Kapodistri an University of Athens, Greece	6.6 Role in the initiation of smoking (particularly focusing on young people)	PAGE 66 LINES 47-48 Non-combusted nicotine an as inhaled, transdermal and chewed or aerosolized NRT is well established as a smoking-cessation strategy. Cardiovascular effects of NRT have been studied in smokers and have not been associated with an increased risk of major cardiovascular adverse events .However, NRT are not risk free. Nicotine possesses sympathomimetic effects resulting to increased heart rate, myocardial contractility and vasoconstriction and thus, may cause myocardial ischemia and arrhythmias. However, we should take in account that the long term use of NRT is an approved method for smoking cessation. Emissions from most e-cigarettes, like those from tobacco cigarettes, also contain nicotine but the plasma levels of nicotine rise slowly and peak at a lower level than combustible tobacco . In a meta-analysis of the autonomic cardiovascular effects of e-	Thank you for your comment.
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cigarette use, the acute increase in heart rate and blood pressure after e-cigarette vaping was significantly lower compared to tobacco cigarettes .

Ref:

Mills E.J., Thorlund K., Eapen S., et al. (2014) Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 129:28–41.

Farsalinos, K. E. et al. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci. Rep.* 4, 4133 (2014).

Moheimani RS, Bhetraratana M, Yin F, et al. Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. *JAMA Cardiol.* 2017;2(3):278-284. doi:10.1001/jamacardio.2016.5303

294 Bamberger Claude,Aid uce,France 6.6 Role in the initiation of smoking (particularly focusing on young people)

6.6 Role in the initiation of smoking (particularly focusing on young people)
Most references about the USA and with a bias mixing experimentation and use, and ignoring that as vaping grew, smoking tobacco cigarettes fell historically. Inclusion of figures of vaping that don't relate to nicotine. And strangely some work ignored on European situation, and from national authorities or references.

For example :
German Cancer Research Centre report DKFZ (too big to upload)
https://www.dkfz.de/de/tabakkontrolle/download/Publikationen/sonstVeroeffentlichungen/2020_E-Zigaretten-und-Tabakerhitzer-Ueberblick.pdf

“Even if numerous studies suggest a connection between e-cigarette consumption and smoking, this has apparently only had little and different effects at the population level”
(Reference uploaded)
Chyderiotis et al., 2020; S. Chyderiotis, T. Benmarhnia, F. Beck, S. Spilka, S. Legleye. Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? *Drug and Alcohol Dependence*, 208 (2020), Article 107853, 10.1016/j.drugalcdep.2020.107853.

<https://www.sciencedirect.com/science/article/pii/S0376871620300181>

“Among ever-smokers, adolescents who declared having ever used e-cigarettes were less likely than those who did not to transition to daily smoking at 17.”
Those studies, based on European facts, as well as national data

Please see Table 1, answer 8 and 11.

from countries with a neutral or positive attitude on vaping, seem to in firm any evidence (strong or moderate or weak) of an increase of smoking because of vaping and instead show a factual picture of a common liability (people interested of smoking are taking a gateway out of smoking). In fact, in France, we observe an historical low in smoking in teens.

295	Sebrie Ernesto, Campaign for Tobacco-Free Kids, United States of America	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>E-cigarette Use Among Middle and High School Students — United States, 2020</p> <p>Page 63, lines 3-5 state: “US current use among high school students increased from 1.5% in 2011 to 20.8% in 2018 (Fadus, et al. 2019, Walley, et al. 2019).” There are more recent youth EC use data available from the US. The studies referenced in the report give the 2018 figure from the National Youth Tobacco Survey (NYTS.) The 2020 NYTS results were released in September 2020, they found that 19.6% of US high school students (3.02 million) reported current use of e-cigarettes. Ref: Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette Use Among Middle and High School Students — United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1310–1312.</p>	See Table 1, answer 11.
296	Posch Waltraud, Austrian Association of Addiction Prevention, Austria	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Aim of Addiction Prevention is to protect people from becoming addicted. Nicotine is highly addictive, regardless of the specific product in which it is consumed. Whether someone starts to use nicotine with an electronic cigarette or a tobacco cigarette does not change the risk of addiction. It is very important to focus on people who start – independent of their concrete age. Almost in all industrial countries initiation age for addiction is shifting backwards. This means there are less children and adolescents who start consuming, but at the same time more young adults who start. This development applies to all legal addictive substances such as alcohol and tobacco and other nicotine products.</p> <p>Apart from this in Austria there is strong evidence that electronic cigarettes are a common “first product” for consuming nicotine for young people. This is reported in ESPAD-study 2019. 39 percent of young people in Austria (aged 14 to 17) already have tried electronic cigarettes. This is an obvious growing proportion compared with ESPAD-study 2015. And 8 percent of young people consumed electronic cigarettes first and started smoking after</p>	No changes in the Opinion needed.

vaping. Each twelfth 14- to 17-year old Austrian came to tobacco cigarette via electronic cigarette.



6.6_Role_in_the_initiation_of_smoking_Elec

297	Schmidt Norbert, Int ernessengemeinschaft E-Dampfen e.V. (IG-ED), Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>P 62 L 48-54 Quoting the uploaded article: "The potential impact suggested by the prospective studies is critical to understand. The proportion of never-smoking youth who try e-cigarettes is small. With only a fraction of those being induced to try smoking (if the gateway theory does hold), the proportion of never-smokers so induced is much smaller still. Further, the percentage of youth who try smoking who go on to become dependent smokers is itself minor. So the aggregate risk implied by the prospective studies is very small. Further – and we consider this very important – the data from large national cross-sectional studies provide no evidence that kids' use of e-cigarettes is increasing smoking. If anything, those data suggest the opposite""</p> <p>Ref: Kozlowski (2017) Adolescents and e-cigarettes: Objects of concern may appear larger than they are?</p>	<p>Thank you for your comment.</p> <p>Please see table 1 answers 1 and 5</p>
298	Schmidt Norbert, Int ernessengemeinschaft E-Dampfen e.V. (IG-ED), Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>P 65 L 54-55 From the uploaded paper: "Relative to vaping tobacco flavors, vaping nontobacco-flavored e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation." Prohibition of flavors would only result in decreased odds for adult quitting, but not change anything for youth behavior.</p> <p>Ref: Friedman (2020) Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation.</p>	<p>See Table 1, answer 7.</p>
299	Dahlmann Dustin, IEV A, Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>P 62 L 48</p> <p>A number of reviews are used to justify the conclusion that there is strong evidence for a gateway effect. The Committee accepts that much of the evidence is from the US, and therefore not directly applicable in the context of the European Union.</p>	<p>Please see table1, answer 5.</p>

However, the committee fails to consider smoking rates among young people in the United States. This is problematic given the stated objective of this section of the report: namely to ascertain whether e-cigarette use among young people is likely to lead to them taking up smoking. If e-cigarettes were providing a gateway to cigarettes, as the committee suggests is evidenced, then US government data would show greatly increased smoking rates in line with the growing popularity of e-cigarettes.

However, US data shows that smoking among young people has actually fallen sharply since e-cigarettes were introduced to the market. Data from the US CDC (attached) shows that from 2013-2015 (during the period where e-cigarettes became popular) experimentation with cigarettes fell from 41.1% to 32.3%; and regular smoking fell from 5.6% to 3.4%. The data from 2019 showed that these numbers remained stable - with 32% having experimented with smoking. If e-cigarettes are a gateway to cigarette smoking in the US, then why is youth smoking falling so significantly there?

P 67; L 26
While the studies noted in this section tend to find that those young people who use e-cigarettes are also likely to use cigarettes at some point, none consider why this might be, simply assuming that if both are used by the same subject then one led to the other. Recent evidence from the US - where the majority of the studies SCHEER has reviewed originate - indicates that the relationship might not be so straightforward in its causality.

Selya et al (2020), attached, undertook a secondary review of the “monitoring the Future” dataset, encompassing 12,421 8th and 10th grade students. The analysis found that e-cigarette use “does not appear to be associated with current, continued smoking...failing to support claims that e-cigarettes have a causal effect on concurrent conventional smoking among youth”.

This study was published after the report from the committee was put to consultation; and given its highly authoritative source of data, It would be appropriate for the Committee to reconsider its

conclusions in light of this new evidence.

P 69, L 34 - 441
As the report notes, the Eurobarometer data looks at experimentation with e-cigarettes among those aged 15-24, which is an odd age range to review. In the majority of EU Member States, the legal smoking age is 18, meaning that 70% of the ages contained in the sample can legally smoke.

Since only 3% of those surveyed in Eurobarometer never smoked before using an e-cigarette, the report should consider the possibility that the majority of those in the 15-24 age group who have tried e-cigarettes are doing so for the right reason: as legal age smokers looking for a less harmful alternative to smoking.

n/a

National data from Member States and other countries where TPD is in force can also be used to consider relevant trends. Irish Government data from 2019 (attached) show smoking rates in the country have fallen from 23% in 2015 to 17% in 2019; concurrent with a rise in e-cigarette use from 3-5%. Less than 1% of non-smokers use e-cigarettes, according to the data.



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Tobacco-free
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6.6 Role in the
initiation of
smoking
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focusing on
young people)

There is also clear evidence that e-cigarettes serve as a gateway for smoking. It is clear from the SCHEER preliminary opinion that use of e-cigarettes has increased markedly among adolescents and that youth appealing flavours play a critical role in initiation. For the role as a gateway, some European studies have been identified through reviews and from other sources (p. 68 of the opinion), but some other relevant studies from EU could also strengthen the opinion. For example, findings from a Finnish longitudinal youth study suggest that experimentation with nicotine e-cigarettes serves as a gateway to subsequent use of conventional cigarettes as well as nicotine e-cigarettes (Kinnunen et al. 2019).

Thank you for your comment.

The data in the opinion shows that among the flavours that appeal

to smokers is tobacco flavour, a flavour not appealing to adolescents without a history of smoking. Tobacco flavour is among the flavours appealing to smokers, but it is not appealing to non-smoking adolescents. It is furthermore clear from the opinion that the evidence for e-cigarettes as a cessation tool for smokers remains weak. One may ask, why are flavours necessary?

See Table 1, answer 7.

Conclusions

Based on the SCHEER preliminary opinion the following conclusions can be drawn:

1. E-cigarettes appeal strongly to adolescents, and youth appealing flavours play a significant role in that appeal. Serious considerations on EU-level measures to improve protection of youth from e-cigarettes should be considered. These considerations should include stricter regulation on youth appealing flavours, including considering banning flavours other than that of tobacco, as well as forbidding advertising, including in social media, and implementing display ban. The regulation of device types and power should also be considered at EU level.

Agreed. No change is needed.

Kinnunen JM, Ollila H, Minkkinen J, Lindfors PL, Timberlake DS, Rimpelä AH. Nicotine matters in predicting subsequent smoking after e-cigarette experimentation: A longitudinal study among Finnish adolescents. *Drug Alcohol Depend.* 2019 Aug 1;201:182-187. doi: 10.1016/j.drugalcdep.2019.04.019. Epub 2019 Jun 19. PMID: 31238240.

301 Lund Karl Erik, Norwegian Institute of Public Health, Norway

6.6 Role in the initiation of smoking (particularly focusing on young people)

Comments from a group of tobacco behavior researchers within the Norwegian Institute of Public Health.

Please see table 1, answer 5.

P 67 L 11 ff: - please note that claims of gateway progression has been scientifically contested. The progression from vaping to smoking observed in longitudinal studies of young people have led to implicit conclusions on causality. Vaping might biochemically or pharmacologically sensitize the brains of users to the rewarding effects of smoking. However, there are plausible competing hypotheses for such a progression, including shared networks and opportunities to purchase, individual characteristics such as genetic predispositions or shared risk-taking susceptibility. Smoking and vaping are very similar behaviours, and the factors that cause people to vape are likely also to cause them to smoke (and vice versa).

Thus, when discussing the gateway mechanism please take into consideration:

i) ..if the criteria to establish causality have been met (the testability of the

gateway hypothesis) (see Etter 2017)
ii) ..the common liability theory – postulating that the association is caused by common underlying causes that increase the use of both substances (see Kim & Selya 2020)
iii) ..the problem of unmeasured residual confounding - taking into account that the association might be due to factors not included in the available longitudinal datasets (Fewel et al 2007)
iv) ..the size of the segment in which a potential gateway mechanism may operate (the proportion of never-smokers who use e-cigarettes). If the size of the population at risk is small, even a strong gateway effect will have moderate impact on smoking incidence.
v) ..the compatibility of the gateway theory with ecological trend data for vaping and smoking – are these correlated (supporting the hypothesis) or inversely correlated (contesting the hypothesis)?

P 67 L 26 ff - as long as the report addresses the gateway hypothesis, it should also give some consideration to the antithesis of the gateway hypothesis; the diversion hypothesis (NASEM 2018, chapter 16, Etter 2017, Kozłowski & Warner 2017)). This concept proposes that because some youth possess an elevated drive to engage in exploratory and risk-taking behavior, the availability of e-cigarettes allows such young people to satisfy their curiosity and drive for novelty seeking without needing to resort to combustible tobacco products to satisfy the desire for exploration.

P 69 L 43 ff: - when discussing renormalization, the report neither address the testability of the hypothesis nor any empirical study explicitly addressing this hypothesis. Please note that as of yet, the evidence for renormalization of cigarette smoking is scarce, and the few studies that exist does not support the hypothesis. Hallingberg et al (2020) found “little evidence that renormalization of youth smoking was occurring”. Booth et al (2019) “observed no evidence that exposure to an e-cigarette advertisement renormalizes or encourages smoking in smokers, non-smokers or e-cigarette users”. A qualitative British study (Brown et al, 2020) concluded “absence of marketing awareness and continued strong disapproval of smoking provides limited support for some of the potential mechanisms through which e-cigarettes may renormalize smoking”. Finally, in a previous assessment of the renormalization concept, Sæbø & Scheffels (2017) identified only one study consistent with a renormalization hypothesis (Goniewicz, et al, 2014).



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302 Csémy
Ladislav,
Harm
Reduction
Academy,
Prague,
Czech
Republic

6.6 Role in the
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smoking
(particularly
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young people)

Thank you for the opportunity to comment on the SHEER report [1]. The report deserves admiration for the great work of the research group in reviewing the very extensive literature that has been published on the issue. We do not dispute most of the conclusions of the SHEER Group, however, we have reservations about two of its conclusions. Unfortunately, these are conclusions that are crucial for the future regulation of e-cigarettes and related public health issues.

One of the conclusions we dispute is the statement, "that there is a strong evidence that electronic cigarettes are a gateway to smoking for young people". We have carefully studied Chapter 6.6 and come to the conclusion that the current state of knowledge - as described here - does not justify talking about strong evidence. In the presented systematic reviews and meta-analyses, only a minority of included are of the RCT study design, even those often suffer from limitations such as sample size, short follow-up, etc. The prevalence of „ever smoked e-cigarettes“ is in some of these reviews very low (e.g. 1.6 % of 91,051 subjects in a review of Zhong *et al.*, 2016 [2]). We agree with the findings of a study by Levy *et al.*, 2019 [3] who pointed to a decline in combustible cigarette smoking among the youth in the US, and also referred to contributing factors. Data from two large international (cross-sectional) studies, ESPAD [4] and HBSC [5], confirm a steady decline in smoking among school-age children and adolescents in European countries, for which, like in the US, is responsible smoking de-normalisation, regulation of availability of tobacco products for under-aged, shifts in young people's leisure preferences, etc. These are only cross-sectional studies where we cannot draw causal conclusions, but the fact that at a time of rapidly growing experience of young people with e-cigarettes, the use of combustible cigarettes is declining among them, leads us to considerable doubts as to whether the effect of e-cigarettes can be so crucial on initiating juvenile smoking.

We cannot agree with the conclusion, "that there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate".

The SHEER researchers, in Chapter 6.7, report the results of two recent RCT studies [6, 7], well controlled, with a relatively long follow-up, and a large sample size. Both of these studies favours the use of e-cigarettes in withdrawal over NRT or placebo, and are newer and methodologically better designed than studies included in older review studies. Nevertheless, without much logic, the SHEER group refers to the conclusions of the Surgeon general's Report on the Smoking Cessation [8], and more or less automatically adopts them.

We are deeply concerned that these two conclusions of the SHEER Group will, in turn, 1) influence the regulation of e-cigarettes in Europe for a long time, and 2) will hamper the development of harm reduction approaches to

Please see Table 1, answer 5.

smoking cessation. The adverse effect will be a slowdown in the transition of cigarette smokers to products with a less risky health profile than combustible cigarettes. The decline in mortality from tobacco-related diseases will slow down and the economic burden of smoking on European societies will not diminish. We doubt this is what we should strive for in Europe.

303	Sweeney Damian ,NNA Ireland ,Ireland	6.6 Role in the initiation of smoking (particularly focusing on young people)	Page 62 line 48 to page 64 line 27	<p>The gateway theory is an artefact of the US ‘war on drugs’ and has no basis in science as it cannot be tested or demonstrate with epidemiological studies. Pooled results show an association but fail to show causality. The common liability factors have not been properly accounted for or in some cases even considered.</p>	Thank you for your comment.
			<p>If a gateway effect was happening, we should see a perceptible rise in smoking prevalence. However, since the advent of e-cigarettes over 10 years ago, smoking prevalence has fallen at an accelerate rate.</p>	Please see Table 1, answer 8.	
			<p>SCHEER examines the phenomenon of e-cigarette use among young populations using mostly studies from the US which SCHEER admits may not reflect the situation in the EU. Eurobarometer studies cited show youth use is mostly experimental and short lasting. Mostly among existing smokers and former smokers, “daily use ranged from 1% to 2.9%. It also showed a higher prevalence of electronic cigarette use among males, adolescents and young adults, smokers of conventional cigarettes, and former smokers (Kapan, et al. 2020).” SCHEER also acknowledged that the most frequently mentioned reason for using electronic cigarettes was to stop or reduce tobacco consumption.</p>		
			<p>The possibility of a gateway is not proven or even demonstrate as a real risk. The SCHEER has failed to show any increase in smoking prevalence either due to the use of e-cigarettes or a decline in cessation attempts. The SCHEER acknowledges there was a decline in youth smoking during the same timeframe as there was an increase in youth e-cigarette use in the USA (page 17 lines 30-32). If the SCHEER is of the opinion that there is strong evidence that electronic cigarettes are a gateway to smoking/for young</p>	Please see Table 1, answer 5.	

			<p>people, they have failed to provide any evidence of such gateway and also fail to show any decline or reduction in cessation by current smokers.</p> <p>In the UK, where e-cigarettes have been embraced by tobacco control, SCHEER admits that youth use among non-smokers is almost non-existent. This positive attitude towards e-cigarettes in reducing the harms of smoking should be adopted throughout the rest of Europe, rather than a prohibitionist approach, and treating e-cigarettes the same as combustible tobacco, that is advocated for in the EHN opinion piece. If reducing the harms from smoking is the goal, then prohibition will not achieve this.</p>	
304	Sweeney Damian,N NA Ireland ,Ireland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Flavors.</p> <p>6.6 Page 64 line 34 to page 66 line 3 SCHEER seems to misunderstand the role of flavors in e-cigarettes. Citing the fact that candy and fruit flavors were associated with decreased harm perception is not a negative aspect. As SCHEER has shown e-cigarettes offer a reduced harm product compared to smoking, this perception is correct. SCHEER has already failed to show any harm from use of e-cigarettes that is increased over smoking. The fact these flavors categories convey that information is a positive aspect.</p> <p>The statement that “Adolescents consider flavour the most important factor trying electronic cigarettes” is contradicted by several papers referenced by SCHEER which show curiosity as the most cited reason for trying e-cigarettes. E.g. page 63 line 26, 27, 28. “manufacturing labels are not always comprehensive in regard to e-liquid constituents and therefore might not alert the consumer to the potential for harmful effects (Sood et al., 2018).”</p> <p>No mention of the fact that all e-liquid must by law carry warning labels. This claim that labels do not convey sufficient indication of possible harms is inaccurate</p> <p>According to the EHN, the fact that people, and particularly young people who have never smoked, are increasingly taking up electronic cigarette use deserves much attention as they are at substantial risk of becoming regular cigarette smokers. Again, this is opinion, no substantial risk has been shown, nor has any substantial increase in regular use of e-cigarettes by never</p>	<p>See Table 1, answers 7 and 1.</p> <p>Please see Table 1, answer 7.</p> <p>The SCHEER has changed the sentence to “Adolescents consider flavour the most important e-cigarette attribute in trying electronic cigarettes”</p> <p>It is true that e-liquids must carry labels, but also in the EU these are not always comprehensive or correct regarding the constituents present in the liquid. The opinion of the EHN is a fact, and important in this section discussing flavors.</p> <p>See Table 1, answers 1 and 7.</p>

smoker young people been shown. SCHEER references (Meernik et al. 2019). “Flavours decrease harm perceptions and increase willingness to try and initiate use of electronic cigarettes. Among adults, electronic cigarette flavours increase product appeal and are a primary reason for many adults to use the product.”

Any interference with this aspect of the e-cigarette product range risks reduced uptake by smokers and will not have an effect on youth use.

305	Sproga Maris, Smoke Free Association of Latvia, Latvia	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Page 52, lines: 13-49</p> <p>The SCHEER opinion does not mention the vital role of e-liquid flavors in switching adult smokers to less harmful vaping products. It focuses only on the enhanced attractiveness for youth - this view is not supported by available evidence from the EU.</p> <p>RIVM publication (Romijnders 2019) demonstrates that among participants who reported to never have smoked and never have used an e-cigarette the majority (68%) of the participants were not interested in trying a flavored e-cigarette, and discusses the importance of flavors for adult smoker switching “. . . the importance and complexity of regulating e-liquid flavors in a way that both the decision to switch towards vaping (for smokers) and the decision to refrain from vaping (for never-users) are supported. Ideally, regulation should allow marketing of e-liquid flavors that stimulate smokers and dual users to keep or start using e-cigarettes. To make never-users more negative about and keep them from using e-cigarettes, product appeal should be reduced by, for example, restricting the marketing and promotion of e-liquid flavors that they find particularly appealing.”</p> <p>This should also be reflected in the SCHEER opinion. https://www.researchgate.net/publication/337460582_E-Liquid_Flavor_Preferences_and_Individual_Factors_Related_to_Vaping_A_Survey_among_Dutch_Never-Users_Smokers_Dual_Users_and_Exclusive_Vapers</p>	<p>See Table 1, answers 1 and 7.</p> <p>On the other hand, 32% expresses interest in trying a flavour, which is concerning.</p>
306	Bates Clive, Counterfactual	6.6 Role in the initiation of smoking	<p>The preliminary report does not cite the most up to date and credible review of studies relevant to the role of e-cigarettes in the initiation of smoking. This is:</p>	<p>Please see table 1 answers 1 and 5</p>

Consulting (particularly
Limited, focusing on
United young people)
Kingdom

Chan GCK, Stjepanovic D, Lim C, Sun T, Shanmuga Anandan A, Connor JP, et al. Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*. 2020 Sep 4; <https://doi.org/10.1111/add.15246>

This review correctly recognises the methodological challenge of clearly distinguishing between a causal "gateway effect" and confounding by "common liabilities". The SCHEER preliminary opinion does not adequately recognise these challenges, Chan et al draw a very different conclusion to that drawn by SCHEER.

The preliminary opinion abstract summarises the SCHEER conclusion:

"Regarding the role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people, the SCHEER concludes that there is STRONG evidence that electronic cigarettes are a gateway to smoking for young people."

This conclusion and the confidence expressed in it are unsupported by any evidence and convincingly refuted by the analysis in Chan et al.

I include the abstract of Chan et al. below and attach the full study as an upload:

Background and Aims
Studies have consistently found a longitudinal association between e-cigarette use (vaping) and cigarette smoking. Many have interpreted such association as causal. This systematic review and meta-analysis evaluated the plausibility of a causal interpretation by (1) estimating the effect of adolescent vaping on smoking initiation, adjusted for study quality characteristics, (2) evaluating the sufficiency of adjustment for confounding based on the social development model (SDM) and the social ecological model (SEM) and E-value analyses and (3) investigating sample attrition and publication bias.

Methods

Systematic review and meta-analysis of longitudinal studies that examined the association between e-cigarette use at baseline and smoking at follow-up. Participants were non-smokers aged < 18 at baseline.

Results

Meta-analysis of 11 studies showed a significant longitudinal association between vaping and smoking [adjusted odds ratio (aOR) = 2.93, 95% confidence interval (CI) = 2.22, 3.87]. Studies with sample sizes < 1000 had a significantly higher odds ratio (OR = 6.68, 95% CI = 3.63, 12.31) than studies with sample sizes > 1000 (OR = 2.49, 95% CI = 1.97, 3.15). Overall, the attrition rate was very high (median = 30%). All but one study reported results from complete sample analysis, despite those dropping out having higher risk profiles. Only two studies comprehensively adjusted for confounding. The median E-value was 2.90, indicating that the estimates were not robust against unmeasured confounding.

Conclusions

There is a longitudinal association between adolescent vaping and smoking initiation; however, the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders.

Ref:

Chan et al (2020). Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. *Addiction*. 2020 Sep 4. DOI: 10.1111/add.15246

307 Olteanu Vlad, Juul Labs Inc., Belgium
6.6 Role in the initiation of smoking (particularly focusing on young people)

We question why the majority of the cited literature relates to only US products, which are neither TPD-compliant nor available in the EU. Quotes are lifted directly from review articles that include very little original synthesis (Walley, 2018) or are irrelevant to e-cig use (Hoffman, 2016) and much of the relevant literature has been omitted. The assertion on Pg 70, ln 12, that there is strong evidence that e-cigs are a gateway to smoking/for young people is not borne out by the evidence. Despite a reliance on US literature, there is no reference to decreases in smoking in the US, as vaping increases,

See Table 1, answer 8.

Please see Table 1, answer 5.

including with adolescents. NASEM 2018 reported that although e-cig use increases the likelihood of ever trying a cigarette, this did not cause an increase in smoking but a rapid decline in adolescent smoking. Two key studies omitted here report that there is “little evidence that renormalisation of youth smoking was occurring during a period of rapid growth and limited regulation of e-cigarettes from 2011 to 2015” in the UK (Hallingberg 2020) and that smoking prevalence among UK youth decreased even further from 2018-19, even as vaping Pg 66, Ln 12 states that ‘the high concentrations of nicotine in electronic cigarettes are of major concern’. Smoking is a major concern, and while nicotine is an addictive component, the harm of smoking is caused by other constituents. E-cigs provide nicotine without these harmful constituents, thereby preventing most of the harm. But to successfully compete with cigarettes, e-cigs must deliver sufficient nicotine. Most research suggests that this is not the case at nicotine concentrations permissible in the EU. O’Connell et al, cited on Line 35, reports that e-cigs with nicotine levels twice that permissible in the EU (myblu 40mg) delivered approximately 33% less nicotine to the user than a combustible cigarette. A TPD-compliant version (myblu 16%) delivered less than half that of a combustible cigarette. The review cited to suggest that adolescents who vape are exposed to more nicotine than those who smoke combined results from two different studies, by different investigators, and using different study protocols. In one study, the values used are not published, cannot be verified and are not accessible in the supplementary files. Flavours are extensively discussed on pages 64-66. While the summary states that: ‘Among adults, electronic cigarette flavours increase product appeal and are a primary reason for many adults to use the product’, this section reviews little relevant adult literature. Nor does the summary statement comport with data demonstrating that the primary reason for adults to use e-cigs is as an alternative to cigarettes (Nicksic, 2019 and Patel, 2016). While smokers generally start vaping using tobacco flavours, it has been demonstrated that, over time, flavour preferences change to non-tobacco flavours, particularly dessert or sweet flavours. A study by Gendall, 2020, showed that for adult smokers who partly or completely switched to e-cigs, the most preferred flavour of e-liquid was fruit. Tobacco and mint/menthol

See Table 1, answer 1. Furthermore, nicotine is a toxic and addictive component, so a compound of concern.

represented 29% of preferred flavours of successful switchers; other flavours represented 71%. A randomised controlled trial (Hajek et al. 2019) in the UK showed that e-cigs are twice as effective as NRTs at helping smokers quit. The same study showed that smokers initially given tobacco flavoured e-liquids chose other flavours in significant numbers when allowed to choose. By the end of the study, tobacco and menthol represented ~41% and other flavours represented ~59% of product use. Together these data suggest that, rather than causing people to start vaping, flavours keep smokers who decide to vape away from cigarettes. Please respect copyrights of uploaded studies..

Ref:

Gendall P, Hoek J Role of flavours in vaping uptake and cessation among New Zealand smokers and non-smokers: a cross-sectional study. Tobacco Control Published Online First: 14 February 2020. doi: 10.1136/tobaccocontrol-2019-055469 <https://tobaccocontrol.bmj.com/content/early/2020/02/14/tobaccocontrol-2019055469>

Hajek (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. DOI: 10.1056/NEJMoa1808779

National Academies of Sciences, Engineering, and Medicine. 2018. Public health consequences of e-cigarettes. Washington, DC: The National Academies Press. doi: <https://doi.org/10.17226/24952>

Nicksic et al (2019) Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study. doi:10.1016/j.addbeh.2019.01.037.

Patel et al (2016). Reasons for current E-cigarette use among U.S. adults. doi:10.1016/j.yjmed.2016.09.011

308	Clark Alex, The Consumer Advocates for Smoke-free Alternatives Association (CASAA), United States	6.6 Role in the initiation of smoking (particularly focusing on young people)	Pg.	64	-	Lines	12	-	14
			Pg.	65	-	Line	12		
			Pg.	66	-	Line	29		
			Pg.	67	-	Line	4		
			Throughout the SCHEER report, a “popular pod device with a 76% US-market share” is referenced. The SCHEER statement lacks context. The penultimate source referenced by Fadus, et al contextualizes this number by noting that JUUL’s market share is only measured as a percentage of Neilson-tracked retail channels. There remains a large segment of the vapor industry that is not tracked by Neilson and is estimated to make up 30% to >50% of the overall nicotine vapor market. "E-cig category dollar sales were \$408.5MM this period implying about ~\$4.6B annual retail sales in Nielsen-tracked channels (vs \$3.3B in 2018). Considering Nielsen underestimates and doesn’t capture all of the channels where e-						

This has been replaced throughout the report by a ‘large market share’.

cigs/vapor products are sold such as online, vape shops, etc, we estimate the total category will reach approximately \$9.0B by the end of 2019 (vs ~\$7.0B in 2018)."

Ref:

Herzog, Bonnie, and Patty Kanada. Wells Fargo, 2019, pp. 11, Nielsen: Tobacco All Channel Data Thru 9/7 - Cig Vol Declines Hold Steady.

309	Vuerich Michela, A NEC, European Consumer voice in standardisation, Belgium	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>6.6 Role in the initiation of smoking (particularly focusing on young people)</p> <p>Page 68, lines 35-45: SCHEER just briefly mentions the literature which does not support the gateway theory without any arguments why SCHEER considers these contradictory positions pointing e.g. to confounding factors as inadequate. This looks very much like a preconceived opinion. As mentioned already in an earlier comment we wonder why adolescents switch to non-flavoured conventional cigarettes if flavours are so attractive. Also the observation that the prevalence of smoking is decreasing (as stated by SCHEER) when e-cigarette use was strongly increasing does not really support the theory – in fact, the strong increase in e-cigarette use would have had a measurable impact on the decrease of smoking. We can expect that many of the young people who are attracted by e-cigarettes and move to smoking later might have gone directly to smoking in case e-cigarettes were not available. If e-cigarettes were to be banned (or strongly discouraged) this might lead to a strong shift towards smoking. Also there is a move in the opposite direction – people who quit or reduce smoking in favour of e-cigarettes. All these aspects need to be reflected before declaring "strong evidence" for the theory.</p>	Please see table 1, answer 5.	
					
			ANEC-PT-2020-CEG-004ANEC_Comments		
310	Woessner Julie, International Network of Nicotine Consumer Organisations	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>See our comment in the TERMINOLOGY section about the gateway hypothesis.</p> <p>Page 62 / Lines 51-54</p> <p>The SCHEER opinion draws upon only seven research papers dated between 2016-19 to assist their assessment and noted that the majority had been carried out in the US. Whilst acknowledging that US data may not necessarily reflect the 'exact' situation in the EU,</p>	See Table1, answer 1.	Please see table 1, answer 8.

(INNCO),
Swiss
based
association
with 35
orgs all
over the
world and
15 from
the EU

they concluded that “trends coming from the US frequently impacted European markets.”

We respectfully submit that regardless of SCHEER’s efforts to consider and compare US data against information from the Eurobarometer, any attempt to achieve an accurate and verifiable assessment of the overall risk posed to young people living within the EU community is likely to be flawed for the following reasons:

Unlike the EU which adopted the TPD2 regulations in 2014, the US has yet to impose a federal framework of uniform standards, effective regulation and consistent guidelines on e-cigarette products.

Perception, awareness, attractiveness and initiation of e-cigarettes are influenced at national levels by a variety of external factors and vary widely amongst different populations in the EU and US States. These include accessibility, cost, the adoption and enforcement of proportionate regulation and notably the overall standpoints adopted by their individual governments and ‘messages’ relayed by Health Ministries and tobacco control NGOs.

For at least the last four years, the US public, particularly schoolchildren and young people, have been bombarded consistently with alarmist (and in some cases misinformed) public health/media campaigns, educational interventions and parent group lobbyists focusing on the dangers and ‘attractiveness’ of e-cigarettes and the ‘intentional’ marketing of flavours to hook young people. To assess the experience of US youth regarding e-cigarettes, including current consumption rates, and equate concomitant risks to European countries is, in our opinion, likely to prove incongruous.

In order to evaluate risks of youth initiation on the basis of proportionate risk, we consider it incumbent upon SCHEER to focus their assessment of youth smoking initiation based on empirical data of youth smoking rates and e-cigarette use over a defined period obtained from individual countries within the EU referencing the most recent data on youth smoking rates within the

EU.

If no generic increase is established, it is an indication that young people's use of e-cigarettes has not resulted in their transitioning to smoking tobacco.

We consider the SCHEER opinion that there is strong evidence that electronic cigarettes are a gateway to smoking for young people is not substantiated by the evidence provided and request that SCHEER consider downgrading the risk to reflect a more accurate assessment in light of J-F Etter, Gateway effects and electronic cigarettes, Addiction, 2017.

Ref:

Etter (2017). Gateway effects and electronic cigarettes. doi:10.1111/add.13924

SCHEER should define the terms "adolescents", "young adults", "youth", "young people", "young", and "children" to help clarify their discussion and analysis. On page 63, line 12, "young people" is defined as ages 15-24 for purposes of the Eurobarometer 458 data, but there is no indication as to whether this age range is consistently applied for all instances of the phrase "young people." "Young adults" is defined as ages 18-25 at p. 63, lines 23-24, but it is not clear whether that is particular to the Kinouani, et al. study or whether that is a definition that is consistently used throughout this section.

In addition, we note that "adolescents can refer to people between the ages of 10 and 19, which provides substantial overlap if a definition of "young people" includes persons between the ages of 10 and 24, and some overlap with "young adults" if that term is understood to mean ages 18-25.

This failure to properly identify age ranges leads to lack of clarity and some confusion. For example, page 65, lines 5-7, SCHEER cites Zare, et. al for the proposition that "Adolescents consider flavour the most important factor [in] trying electronic cigarettes and were more likely to initiate using through flavoured electronic cigarettes." However, SCHEER also notes that "curiosity is the most frequently reported reason for initiating the use of e-cigarettes in young adults". (page 63, lines 26-28)

Please see table 1, answer 5.

311 Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU

6.6 Role in the initiation of smoking (particularly focusing on young people)

The SCHEER generally used the terms indicated in the publications.

The SCHEER changed the sentence to "Adolescents consider flavour the most important **e-cigarette attribute** in trying electronic cigarettes"

Page 63 / Lines 4-6
 SCHEER cites Fadus, et al. 2019 and Walley, et al. 2019 for the proposition that there was a significant increase in US current use among high school students (1.5% in 2011 to 20.8% in 2018). The most recent data from the 2020 National Youth Tobacco Survey (NYTS) in the US reports a marked decline in youth use of e-cigarettes. For example, among high school students, last 30-day use is down from 27.5% in 2019 to 19.6 percent 2020, and self-reported use of e-cigarettes likewise decreased among middle school students in that same time period, from 1.24 million in 2019 to 550,000 in 2020. Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. E-cigarette Use Among Middle and High School Students — United States, 2020. MMWR Morb Mortal Wkly Rep 2020;69:1310–1312. DOI: <http://dx.doi.org/10.15585/mmwr.mm6937e1>

Page 64 / Lines 37-38
 The phrase “youth-appealing flavours” to describe flavours “ranging from fruits, desserts, candy, and soda to traditional tobacco.” The phrase “youth-appealing flavours” is inappropriate. Leaving aside the fact that adults enjoy flavours as well and routinely cite flavours as a significant factor in their success in quitting smoking using e-cigarettes, the breadth of the range of flavours cited makes it seem as if every single flavour--including traditional tobacco--is “youth appealing.”

Page 65-66 / Lines 52-2
 SCHEER cites the European Heart Network, however, SCHEER fails to note that the European Heart Network paper relies heavily on the US NASEM report. This gives the impression that this is European data, but it is not.

Ref:
 Wang et al (2020). E-cigarette Use Among Middle and High School Students US 2020. MMWR. Morbidity and Mortality Weekly Report. September 18, 2020 / Vol. 69 / No. 37

Page 66 and 67, in discussing “addiction” in connection with nicotine, see our comment in TERMINOLOGY about addiction/dependency definition.

The phrase “youth-appealing” was removed.

The European Heart Network is a Foundation that plays a leading role in the prevention and reduction of cardiovascular diseases, through advocacy, networking, capacity-building, patient support, and research, throughout Europe. Opinions and annual reports developed by the EHN are based on extensive literature search and in-house, as well as public discussions, and assist in establishing EU policies affecting cardiovascular health.

312 Woessner 6.6 Role in the Julie, Internal initiation of ational smoking

Network of (particularly
Nicotine focusing on
Consumer young people)
Organisations
(INNCO),
Swiss
based
association
with 35
orgs all
over the
world and
15 from
the EU

Page 67, lines 11-24 and elsewhere
We question to what extent (if any) SCHEER has considered other scientific hypotheses with regards to this issue, for instance “common liability hypothesis”, in this data? Smoking rates are in full decline, including the adolescent group, since the electronic cigarette appeared. See NIDA. 2019, December 18. Monitoring the Future Survey: High School and Youth Trends DrugFacts. Retrieved from <https://www.drugabuse.gov/publications/drugfacts/monitoring-future-survey-high-school-youth-trends> on 2020, October 26

Thank you for your opinion.

Page 69 / Lines 43-45
Societal disapproval is basically the stigmatisation of a part of the population and it raises human rights concerns. Vaping not being smoking, it can hardly renormalize smoking and could even accelerate the denormalization by showing people who still smoke that they can use safer alternatives.

Page 69, lines 45-46
SCHEER cites concerns regarding renormalizing of smoking leading to an increase in smoking (presumably assuming that normalizing e-cigarette use would normalize smoking, something for which no basis is asserted). We bring to SCHEER’s attention a recent study benefiting from the use of a large, nationally representative sample of school-age children from England, Scotland and Wales, covering a long time period (17 years). (Hallingberg B, Maynard OM, Bauld L, et al., “Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England,Scotland and Wales, Pub: April 2019 BMC Journal. Specifically, the authors note, “The renormalisation hypothesis assumes that growing prevalence and visibility of e-cigarette use will reverse tobacco control successes through increasing the extent to which smoking is once again seen as a ‘normal’ behaviour, accepted and accommodated by the non-smoking majority, including young people. However, the hypothesis that e-cigarettes will renormalise smoking in young people is premised on an assumption that tobacco use and e-cigarette use are viewed by

Please see Table 1, answer 5.

young people as sufficiently similar for one to renormalise the other.”

Hallinberg et al. further note, “By contrast, some argue that e-cigarettes may denormalise smoking through social display of an alternative behaviour, leading to displacement away from tobacco use for some young people who would otherwise have become smokers.”

Ref:

Monitoring the Future Survey: High School and Youth Trends 2019

Page 62 line 45 (and section 6.7, and abstract lines 42-47):

313 Giangreco Daniela, Italian League against Cancer - Milan (LILT MILANO-MB), Italy

6.6 Role in the initiation of smoking (particularly focusing on young people)

According to a systematic review and meta analysis study carried out by researchers from the University of Bristol and published in the peer review of Tobacco control, young people who use electronic cigarettes are more likely to smoke conventional cigarettes. The 17 meta-analysis studies, considering confounding factors, show that non-smokers who had tried e-cigarettes are 2.9 times more likely to go on to smoke tobacco (adjusted odds ratio 2.92, 95% confidence interval 2.30 to 3.71).

[SEE UPLOADED FILE: “University of Bristol”]

Also electronic cigarettes are unlikely to discourage conventional cigarette smoking among the population in general. A number of Italian annual representative cross-sectional studies carried out over a period of four years (2014 - 2018) show that among all Italians reporting to be ever electronic cigarette users, those (re)starting smoking after using e-cigarettes outnumber those who stop smoking after using e-cigarettes

Liu X, Lugo A, Davoli E, Gorini G, Pacifici R, Fernández E, Gallus S. Tobacco Control. 2020 Mar;29:148-152

Chapter 6.7

Also another Italian study shows that in dual smokers e cigarettes are used when traditional tobacco cigarettes are banned. Among 395 e-cigarette users, 71.5% used e-cigarettes in at least 1 smoke-free indoor environment, proving that people resolve to e-cigarettes when tobacco smoking is prohibited (Gallus S, Borroni E, Liu X, et al. Electronic cigarette use among Italian smokers: patterns, settings, and adverse events. Tumori. 2020 Apr 26:300891620915784).

See Table 1, answer 2.

			<p>Ref: Khouja et al (2020). Is e- cigarette use in non- smoking young adults associated with later smoking? A systematic review and meta- analysis doi:10.1136/tobaccocontrol-2019-055433 Gallus et al (2020). Electronic cigarette use among Italian smokers: patterns, settings, and adverse events. DOI: 10.1177/0300891620915784</p>	
314	Lowenstein, William, S OS addictions, France	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>page 62, line 45-57 page 63, line 1-43 It is suggested to complete this part of the opinion by data from European studies which show poor attractiveness of electronic cigarettes for adults and young people who have never smoked.</p> <p>In England, according to the report “Vaping in England: an evidence update including mental health and pregnancy, March 2020 vaping “ remains most common among smokers and former smokers, with less than 1% of people who have never smoked currently vaping”.</p> <p>The report also reveals low and stable prevalence of vaping among young people. “Current vaping prevalence (weekly or less than weekly) among young people in England has remained reasonably steady with the best recent estimates putting it at 6% of 11 to 15-year-olds in 2018 and 5% of 11 to 18-year-olds in 2019. Older children are more likely to vape. Current use among 11-year-olds was estimated at less than 1% in 2018, compared with 11% of 15-year-olds. Current vaping is mainly concentrated in young people who have experience of smoking. Less than 1% of young people who have never smoked are current vapers</p> <p>No surveys reported much increase in vaping prevalence”.</p> <p>In France, an article published by the High Council for Public Health provides an overview of latest available data about the situation of young people vaping in France. It concludes that experiencing e-cigarettes has widely spread among young people. Yet its regular use is limited and the cigarette remain the leading psychoactive product which is used on a daily basis. Moreover, the percentage of young people who use neither e-cigarettes nor cigarettes is on the increase.</p>	See Table 1, answer 11.

References:

McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England. London: Public Health England. <https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march-2020/vaping-in-england-2020-evidence-update-summary#vaping-among-adults>

L'usage de la cigarette électronique chez les adolescents en France : où en sommes-nous ?

Sandra Chyderiotis, Olivier Le Nézet, Éric Janssen, Alex Brissot, Antoine Philippon, Stanislas Spilka

<https://www.hcsp.fr/explore.cgi/Adsp?clef=170>

315 Pooler Marc,UK Vaping Industry Association,United Kingdom
6.6 Role in the initiation of smoking (particularly focusing on young people)

On Nicotine: Page 66, line 11-13 – The Opinion states that the ‘high concentrations of nicotine in e-cigarettes are of major concern’. - What is of concern is smoking and the high prevalence in the EU, including some countries where almost 40% of the adult population still smoke (8).

See Table 1, answer 1.

- E-cigarettes are one of several types of nicotine containing products intended as alternatives to combustible cigarettes – as a gateway out of, not in to smoking. The National Institute for Health Research found that vaping was twice as effective at helping smokers quit compared with a choice of combination nicotine replacement therapy (9).

- Nicotine-containing products such as medicinal NRTs have been used safely by smokers for more than forty years, but with little success. Queen Mary’s University has found that E-cigarettes are almost twice as effective as nicotine replacement treatments at helping smokers to quit (10).

- A 2019 randomised trial of e-cigarettes and nicotine-replacement therapies which used a nicotine e-liquid of 18mg per millilitre found that e-cigarettes were more effective for smoking-cessation than nicotine-replacement therapy, when both products were accompanied by behavioural support (11).

On E-Cigarettes as a Gateway: In the UK, Public Health England recently outlined that ‘evidence does not support the concern that e-cigarettes are a route into smoking among young people’ (12) and a poll the same year also found that nearly two thirds of vapers (68%) said they never

See Table 1, answer 5.

thought they would quit smoking until vaping came along (13).

Page 66, line 1- 10 – The suggestion that e-cigarettes act as a ‘gateway to combustible cigarettes’ is not borne out by the evidence.

- In a report in 2017 it was reported that ‘surveys across the UK showed a consistent pattern: most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low.’ (14)

- A rise of vaping in the UK and US has been accompanied by reduction in smoking prevalence.

- For example, a National Institute of Health funded study showed that the increase in vaping in the US has not resulted in an increase in smoking but rather a sharp decline. It concluded that the first statistically significant increase in population smoking cessation in the US in nearly 25 years was associated with a substantial increase in the use of e-cigarettes by US adults. This study, involving hundreds of thousands of participants, showed that e-cigarettes increased smoking cessation across subgroups and concluded that it is remarkable that this is the kind of data pattern that was predicted but never achieved at the population level for NRTs or varenicline. (15)

- Overall, there is no compelling evidence that vaping causes smoking.

- (8) Our World in Data, 2019
(9) NIHR/Cancer Research UK, April 2019
(10) Queen Mary’s University, 2019
(11) Hajek, 2019
(12) Public Health England, 2020
(13) OnePoll, 2019
(14) Bauld et al, 2017
(15) Zhu et al, 2017

316 Moiroud Jean, Fédération Interprofessionnelle de la Vape (FIVAPE), France

6.6 Role in the initiation of smoking (particularly focusing on young people)

Addictiveness and attractiveness related to ingredients – flavours (p. 64 lines 29-57; p. 65 lines 1-57; p. 66 lines 1-2):

- Importance of the variety of flavours as a necessary asset for the effectiveness of the product.
- Explain that the "increased attractiveness" referred to in the report is a value judgment and that a deliberately unattractive product would be ineffective in tobacco control.
- Highlight that vaping presents an effective solution to individually reduce the risk of the 26% of active smokers in the EU.

See Table 1, answers 1 and 7.

- The public health mechanism of vape is to present smokers with a credible and enviable alternative.
- The necessary mix includes taste, the effectiveness of nicotine alone in managing cravings, the user's perception of risk, price, accessibility, form and marketing approach.
- Reducing each of these criteria would degrade the vaping proposal and undermine its public health potential. See the Royal College of Physicians' article, section 12.10 page 187.

P. 64, line 34: regarding flavours, this study should be considered in this part:
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787> "Relative to vaping tobacco flavours, vaping non tobacco-flavoured e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation."

Addictiveness and attractiveness related to ingredients – nicotine (p. 66 lines 5-57; p. 67 lines 1-9):

- Bring a different perspective on how nicotine is addressed in the report. Scheer talks about nicotine addiction without talking about the role and interest that this condition can have.
- The role of nicotine substitutes has been proven to be an effective lever for smoking cessation. The question of nicotine addiction does not arise, or very little about chewing gum and patches. Why should vapes suffer from this concern?
- Moreover, limiting, banning or taxing vaping products for these reasons would only increase tobacco consumption.
- Distributing the total number of smokers and converting some of them into simple nicotine addicts is an advance in public health and a sustainable risk reduction objective.

See Table 1, answer 1.

Role as a gateway product or renormalisation of traditional tobacco smoking (p. 67, lines 11-57; p. 68; p. 69 lines 1-8): FIVAPE would like to stress its concern regarding SCHEER's view on this section. SCHEER members and experts have adopted an inexplicable position which contradicts many of their peers and other scientific or medical bodies.

Please see table 1 answer 5

Furthermore, the reasons that push a person to smoke can be the same as for an entry into vaping: family, family environment, social status, school failure, mental health, genetics etc.

It is therefore impossible not to find a link.

See for example the conclusion of Chan GCK et al. 2020 (link here: <https://onlinelibrary.wiley.com/doi/abs/10.1111/add.15246>), which is much more moderate than the SCHEER's conclusions.

The mere concept of "gateway effect" is dubious and its adoption by Scheer is open to criticism. It is of little interest to ask which product - tobacco or vaping products - was first used during adolescence, and it seems impossible to provide tangible elements on this subject.

It should be noted that the PHE report in 2015 simply advised abandoning the use of the gateway terminology. Link thereafter: <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>

It is worth noting that Jarvis et al, 2020 (link here: <https://www.qeios.com/read/745076.5>) have demonstrated the existence of a link between teenage vaping users in the USA and their previous tobacco use. This thus proves that vaping can indeed be used as a gateway from tobacco products..

Ref:

Friedman AS, Xu S (2020). Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

Chan et al. (2020). Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation. <https://onlinelibrary.wiley.com/doi/abs/10.1111/add.15246>

Public Health England report of 2015: "E-cigarettes: an evidence update". <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>

Jarvis et al. (2020). Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA? v.2. <https://www.qeios.com/read/745076.5>

317 Pooler
Marc,UK
Vaping
6.6 Role in the
initiation of
smoking

• Overall, there is no compelling evidence that vaping causes smoking. (16)

See Table 1, answer 7.

Industry Association, United Kingdom	(particularly focusing on young people)	<p>On Flavours: We consider that any ban on flavours is likely to make vaping less attractive to smokers who might otherwise make the switch. In the UK, Public Health England (PHE) found in 2020 (17) that banning flavoured liquids would deter vapers from using vaping products to help them quit or reduce their smoking and that it could push them towards illicit products.</p> <p>The UKVIA has issued guidance to members which aims to strike the right balance between innovative and appealing products which support adult smokers in the transition to a less harmful alternative, whilst not appealing to anyone who does not already smoke or vape or anyone who is under 18. These guidelines state that members must not use flavour names or descriptors that are particularly appealing to youths, or are associated with youth culture, including popular language or expressions, or names which are reminiscent of confectionary disproportionately appealing to children.</p> <ul style="list-style-type: none"> • Adult vapers like and want flavours. Research shows that smokers who switch to vaping typically start with tobacco flavours (18) suggesting that they are using e-cigarettes as a way of quitting smoking, rather than to vape flavours. However, flavour preferences change over time migrating towards sweeter flavours. (19) • A year-long study showed that when smokers who were initially given tobacco-flavour e-liquids were allowed to choose their own, approximately 60% chose non-tobacco or menthol flavours. (20) • A 2013 report concluded ‘Flavours variability should be maintained; any potential future risk for youngsters being attracted to E-Cigarettes can be sufficiently minimized by strictly prohibiting E-Cigarette sales in this population group’. (21) <p>(16) Kozłowski et al, 2017 (17) Public Health England, 2020 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf) (18) Public Health England, 2015 (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733022/E-cigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf) (19) Du et al, 2020</p>
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			(20) (21) Farsalinos et al, 2013	Hajek,	2019	
318	't Hart Emil, Elekt ronische Sigaretten Bond Nederland, Netherlands	6.6 Role in the initiation of smoking (particularly focusing on young people)	Page 52	lines:	13-49	See Table 1, answer 7. On the other hand, 32% expresses interest in trying a flavour, which is concerning, even if the majority is not interested. The majority of the people is also not interested in trying cigarette smoking, but it is still very problematic that many of them do.
			<p>The SCHEER opinion does not acknowledge that e-liquid flavors play a significant role in ensuring that smokers fully switch to e-cigarettes by solely focusing on the attractiveness for youth and potential gateway effect which is not backed-up by evidence from the EU and definitely not support by Dutch data. In that regard a publication by the RIVM – with as a co-author external expert of the currently tabled SCHEER’s opinion Dr. R. Talhout - demonstrates that among participants who reported to never have smoked and never have used an e-cigarette the majority (68%) of the participants were not interested in trying a flavored e-cigarette. In addition, the importance of flavors is discussed in which it was stated that “. . . the importance and complexity of regulating e-liquid flavors in a way that both the decision to switch towards vaping (for smokers) and the decision to refrain from vaping (for never-users) are supported. Ideally, regulation should allow marketing of e-liquid flavors that stimulate smokers and dual users to keep or start using e-cigarettes. To make never-users more negative about and keep them from using e-cigarettes, product appeal should be reduced by, for example, restricting the marketing and promotion of e-liquid flavors that they find particularly appealing.” These conclusions should be reflected in the final opinion of the SCHEER.</p> <p>References: Romijnders, K.A. et.al E-Liquid Flavor Preferences and Individual Factors Related to Vaping: A Survey among Dutch Never-Users, Smokers, Dual Users, and Exclusive Vapers. Int. J. Environ. Res. Public Health 2019;16(23):4661. Published 2019 Nov 22. doi:10.3390/ijerph16234661</p>			
319	No agreement to disclose personal data	6.6 Role in the initiation of smoking (particularly focusing on young people)	P.62, 148:	<p>As the national trade association of electronic smoking producers, ANAFE has always been committed to ensuring that electronic cigarettes are not sold to minors under the age of 18, thus fighting against younger generations’ use. In particular, the Association reports illegal behaviour to the competent authorities, in line with national legislation on the prohibition of sales to minors.</p> <p>Furthermore, the members of the Association have decided to sign a Manifesto, committing to: 1) pursue the protection of minors and</p>		

non-smokers, discouraging them both from the consumption of cigarettes and tobacco and the use of any other product with or without combustion; 2) fight against the sale of electronic cigarettes and e-liquids, with and without nicotine, to minors by promoting awareness of the health risks connected with their consumption, also through its retailers; 3) oppose advertising campaigns containing messages that might lead to believe that the consumption of electronic cigarettes is without risks or has beneficial effects, or with messages deemed to be attractive by minors. In consideration of the Association's important commitment to protecting young people, the Manifesto was supported by the MOIGE (Italian Parents Movement) (doc.31).

P.62, 152: ANAFE does not support the statement that "trends from the USA often affect European markets as well". In fact, the European electronic cigarettes market is completely different from the American one, due to both regulation and consumer trends. For instance, it should be noted that in Europe, due to the current harmonized regulation, there have been no issues of public health related to electronic cigarettes, as happened in the United States, with the so-called "EVALI cases".

P.62, 156: American data that were taken into account are partial, as there is no mention to traditional smoking rates among young Americans. The comparison assumes particular relevance in consideration of the fact that the rationale of the paragraph is to demonstrate the role of electronic cigarettes as a gateway or in initiation to traditional smoking. As a matter of fact, if such conclusion was true, we would have had increasing smoking rates hand in hand with the spread of electronic cigarettes in the market.

However, US data show exactly the opposite. In particular, what emerges from the "Morbidity and Mortality Weekly Report (MMWR) - Frequency of Use Between Middle and High School Student Tobacco Product Users - United States, 2015-2017" is that between 2011 and 2017, current use of cigarettes, cigars, smokeless tobacco, and pipe tobacco decreased significantly among middle and high school students, whereas the use of electronic cigarettes increased significantly from 1.5% to 11.7% (doc. 32).

See Table 1, answer 8.

Aspects of mixing e-liquids at home are addressed in the Opinion.

EVALI cases are outside of the scope of the Opinion. Please see also reply to comment 20.

Among other things, American data also confirm the broader thesis claiming that the new generation products and, in particular, electronic cigarettes do not represent an increase in the supply of nicotine products available to consumers, since they should be considered as alternatives to traditional products that determine different consumption choices compared to the past.

Ref:
Morbidity and Mortality Weekly Report (MMWR) December 14, 2018 / 67(49); 1353–1357
Morbidity and Mortality Weekly Report (MMWR). Frequency of Tobacco Use Among Middle and High School Students — United States, 2014 Weekly October 2, 2015 / 64(38); 1061-1065
MANIFESTO ANAFE (in IT)

320 No agreement to disclose personal data 6.6 Role in the initiation of smoking (particularly focusing on young people)

This is also confirmed at national level, particularly from the latest data published by the Customs Agency, which states that over the last 4 years, the overall demand for tobacco has reduced by about 2.4 million kg, due to the reduction in cigarette consumption (doc. 33). This loss may be due first and foremost to a substitution effect of smokeless inhalation tobaccos, cigarillos and cut tobacco. To sum up, data highlight how electronic cigarettes neither play a gateway role nor initiate to traditional smoking.

To conclude, it seems appropriate to cite the scientific article by prof. Shu-Hong Zhu, where, with reference to the American population, it is stated: "The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level" (doc. 34).

P.63, 128: ANAFE does not fully agree with what the opinion indicates regarding the continuous use of electronic cigarettes. As a matter of fact, from DOXA national data, released by the Istituto Superiore di Sanità on the occasion of the World No Tobacco Day, it emerges that the use of electronic cigarettes leads to cessation, with an increasing percentage of people who quit smoking thanks to electronic cigarettes. DOXA data from 2016 (doc 35) state that those who have quit smoking thanks to the use of electronic cigarettes are 7.7% of Italian vaping users; this figure

grows and reaches 14.4% in 2017 (DOXA 2017 data) (doc. 36) and 17.7% in 2018 (2018 data) (doc. 37).

P.64, 134: Flavours represent an important component of e-cigarettes. As demonstrated by several studies, in particular by the study of the University of Memphis, flavours are fundamental in the process of quitting tobacco and the ban on their sale has only increased the number of smokers (doc. 38).

See Table 1, answer 7.

There are also studies showing the correlation between aromas different from tobacco and smoking cessation; in particular we refer to the study conducted by Prof. Farsalinos, according to which former smokers prefer electronic cigarettes with sweet or fruit flavoured liquids. In general, the attractiveness of flavours must not be considered a danger in itself. On the contrary, they should be evaluated as a factor that allows adult smokers to switch from harmful products such as traditional cigarettes to new technologically advanced products (such as electronic cigarettes) controlled by health authorities and which, according to many studies, imply less risk to human health.

Ref (only in English):

Zhu et al (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population survey. BMJ 2017; 358 doi: <https://doi.org/10.1136/bmj.j3262>

Yang (2020). The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. <https://doi.org/10.1016/j.abrep.2020.100273>

321 No agreement to disclose personal data
6.6 Role in the initiation of smoking (particularly focusing on young people)

P.67, 126: The causal relationship between electronic cigarettes' use and smoking is not so simple and obvious. According to some studies conducted in the United States - the country where this Preliminary Opinion takes so many data and references - the relationship and the role of gateway are not so linear. In particular, we consider the recent data published in a July 2020 study, where electronic cigarettes' use "does not appear to be associated with current, continued smoking [...] failing to support claims that e-cigarettes have a causal effect on concurrent conventional smoking among youth" (doc. 39).

Please see table 1 answers 1, 5 and 8.

P.69, 141: Eurobarometer data analyse an experimentation with electronic cigarettes between 15 and 24 years. The choice of the age

group is controversial as in most European countries, including for instance in Italy, 18-year-olds only are allowed to purchase electronic cigarettes.

p.70, 112: ANAFE believes electronic cigarettes are not a gateway to smoking for young people. This is confirmed by the most recent data published by the Italian Higher Institute of Health which, on the occasion of the World No Tobacco Day 2020, released the usual DOXA survey (doc. 40). Data show that during the months of March-May 2020 (Covid19 lockdown), traditional smokers have decreased compared to the increase in consumers of heated tobacco and electronic cigarettes.

If SCHEER's conclusions were correct, we should have had a higher number of smokers in Italy, considering the increase of electronic cigarettes' users. Instead, Italian data show that: smokers went from 23.3% to 21.9% (1.4% less which corresponds to an estimate of approximately 630,000 fewer smokers). With regard to age groups, about 206,000 young people between 18-34 years old, 270,000 between 35 and 54 years old and about 150,000 between 55 and 74 years have quitted smoking cigarettes. In addition, 3.5% of the population, while not completely ceasing the consumption of tobacco products, decreased the quantity consumed. Electronic cigarette users before the lockdown were 8.1% of the Italian population (18-74 years). During the lockdown this percentage rose to 9.1% with an increase in electronic cigarette users of approximately 436,000 people.

Ref:

Kim (2020). The Relationship Between Electronic Cigarette Use and Conventional Cigarette Smoking Is Largely Attributable to Shared Risk Factors. *Nicotine & Tobacco Research*, Volume 22, Issue 7, July 2020, Pages 1123– 1130, <https://doi.org/10.1093/ntr/ntz157>

322	Pooler Marc,UK Vaping Industry Association,United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	On Page 66, line 11-13 – The Opinion states that the ‘high concentrations of nicotine in e-cigarettes is of major concern’.	Nicotine: Please see table 1 answers 1, 5, 6 and 8
			<ul style="list-style-type: none"> • What is of concern is smoking and the high prevalence in the EU, including some countries where almost 40% of the adult population still smoke (8). • E-cigarettes are one of several types of nicotine containing products intended as alternatives to combustible cigarettes – as a 	

gateway out of, not in to smoking. The National Institute for Health Research found that vaping was twice as effective at helping smokers quit compared with a choice of combination nicotine replacement therapy. (9)

- Nicotine-containing products such as medicinal NRTs have been used safely by smokers for more than forty years, but with little success. Queen Mary's University has found that E-cigarettes are almost twice as effective as nicotine replacement treatments at helping smokers to quit. (10)

- A 2019 randomised trial of e-cigarettes and nicotine-replacement therapies which used a nicotine e-liquid of 18mg per millilitre found that e-cigarettes were more effective for smoking-cessation than nicotine-replacement therapy, when both products were accompanied by behavioural support. (11)

On E-Cigarettes as a Gateway:
In the UK, Public Health England recently outlined that 'evidence does not support the concern that e-cigarettes are a route into smoking among young people' (12) and a poll the same year also found that nearly two thirds of vapers (68%) said they never thought they would quit smoking until vaping came along. (13)

Page 66, line 1- 10 – The suggestion that e-cigarettes act as a 'gateway to combustible cigarettes' is not borne out by the evidence.

- In a report in 2017 it was reported that 'surveys across the UK showed a consistent pattern: most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low.' (14)

- A rise of vaping in the UK and US has been accompanied by reduction in smoking prevalence.

- For example, a National Institute of Health funded study showed that the increase in vaping in the US has not resulted in an increase in smoking but rather a sharp decline. It concluded that the first statistically significant increase in population smoking cessation in the US in nearly 25 years was associated with a substantial increase in the use of e-cigarettes by US adults. This study, involving hundreds of thousands of participants, showed that e-cigarettes increased smoking cessation across subgroups and concluded that

it is remarkable that this is the kind of data pattern that was predicted but never achieved at the population level for NRTs or varenicline. (15)

• Overall, there is no compelling evidence that vaping causes smoking. (16)

(8) Our World in Data, 2019

(9) NIHR/Cancer Research UK, 2019

(10) Queen Mary's University, 2019

(11) Hajek, 2019

(file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Hajek%202019.pdf)

(12) Public Health England, 2020

(13) OnePoll, 2019

(14) Bauld et al, 2017

(15) Zhu et al, 2017

(16) Kozłowski et al, 2017

323 Cattaruzza Maria Sofia, Italian Society of Tobaccology SITAB, Italy

6.6 Role in the initiation of smoking (particularly focusing on young people)

The Italian Society of Tobaccology (SITAB) agree with the SCHEER Report about the gateway role of electronic cigarettes towards smoking initiation in young people. In 2018, Tabaccologia, the scientific journal of SITAB, published the results of a local study conducted in the province of Verona (North Italy) which reported that 50.4% of students (14-17 years old) used e-cig and for 37% of them ie-cig was the first nicotine contact.

This is out of the scope of the Opinion.

(Lugoboni F, Sacconi A. Data on e-cig use from a large cohort of adolescent: a gateway to illicit substance use? Tabaccologia. 2018; 2:20-25)

A great role in the increased use of e-cigs by young people is due to the advertising made by tobacco companies through social media and the promotion of their influencers.

In fact, Facebook and Instagram were recently asked to review their policies to ban the promotion of e-cigs by influencers. Google has also been asked to remove several applications that promote vaping in the Google Play shop.

Perhaps a mention to these social aspects could be included in the report.

Please, have a look at the following links:

<https://www.tobaccocontrolaws.org/litigation/decisions/it-20191115-national-council-of-consumers->
<https://www.asa.org.uk/rulings/british-american-tobacco-uk-ltd-G19-1018310.html>
http://tobaccoendgame.it/archivio_2019/una-petizione-internazionale-ai-capi-dei-social-media-affinche-impediscano-la-pubblicita-del-tabacco/
<https://tobaccoendgame.it/news/la-pubblicita-del-tabacco-continua-su-facebook-e-gli-altri-social-come-funziona/>
<https://tobaccoendgame.it/news/regolamentazione-delle-sigarette-elettroniche-in-italia-1/>
<https://tobaccoendgame.it/uncategorized/sigarette-elettroniche-in-italia-2-ambiguita-e-carenze-della-attuale-regolamentazione/>
<https://tobaccoendgame.it/news/sigarette-elettroniche-3-cinque-proposte-per-migliorare-la-regolamentazione/>

Finally, since e-cigarettes are often used where smoking is prohibited, their use should be banned in all the places where conventional cigarettes are forbidden. This is a very important message to all, smokers and non-smokers, and especially important for young people. (Gallus S, Borroni E, Liu X, et al. Electronic cigarette use among Italian smokers: patterns, settings, and adverse events. *Tumori*. 2020 Apr 26:300891620915784).

324	Juusela Maria, Doctors against tobacco (DAT) Finland, Finland	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Nicotine containing electronic cigarettes do not help in quitting smoking (Fried & Gardner 2020). On the contrary, among young people, who are more susceptible than adults to develop nicotine addiction, electronic cigarettes serve as a gate to smoking (Peterson & Hecht 2017, Walley et al. 2019). Thus, they cannot be regarded as useful products, equivalent to medical drugs, but rather as chemicals.</p> <p>Ref: Peterson et al (2017). Tobacco, E-Cigarettes and Child Health. <i>Curr Opin Pediatr</i> . 2017 April ; 29(2): 225–230. doi:10.1097/MOP.0000000000000456. Fried et al (2020). Heat-Not-Burn Tobacco Products: An Emerging Threat to Cardiovascular Health. October 2020 <i>AJP Heart and Circulatory Physiology</i>. DOI: 10.1152/ajpheart.00708.2020</p>	Thank you for your comment.
325	Froguel Alizee, Cancer	6.6 Role in the initiation of smoking	<p>On e-cigarettes acting as a possible gateway to smoking and/or renormalisation smoking (p67-69):</p>	

Research UK,United Kingdom	(particularly focusing on young people)	Based on the evidence available, Cancer Research UK conclude that there is insufficient evidence that e-cigarettes act as a gateway to smoking for young people.	Please see Table 1, answer 5.
		<p>Research on the gateway effect is also often limited by the difficulty in accounting for common risk factors which may make young people more likely to smoke and vape, meaning the relationship between the two isn't necessarily causal. Whilst many studies attempt to control for this in their analysis, residual confounding often exists.</p> <p>As this report acknowledges (p68, 147-55), most of the research demonstrating a gateway effect of e-cigarette use to smoking comes from analysis of US data which isn't necessarily relevant to other nations with different regulatory environments and should therefore not be used to represent patterns of use elsewhere. In addition, US surveys define "current e-cigarette use" as "use on at least one day in the past 30 days", definitions that fail to distinguish between experimentation and regular use. These broad definitions mean we are unable to ascertain whether the increase in e-cigarette use in young people is due to an increasing number of young people experimenting with these products or whether more people are using them regularly.</p> <p>Much of the research examining the gateway effect which informed the Committee's preliminary opinion is relatively old (pre-2017). Given e-cigarette research is a fast-moving field, it is important that the Committee consider more recent evidence before drawing conclusions as to whether e-cigarettes are acting as a gateway to smoking among young people.</p> <p>There is little evidence that many children in Great Britain are using e-cigarettes. According to a 2019 survey, among children aged 11-18 who have never smoked, only 0.1% of children use an e-cigarette more than once a week and nobody surveyed reported daily use. This coincides with the continuing decline in youth smoking.(1) A 2019 study also found the acceptability of smoking among young people in Great Britain has fallen faster since the introduction of e-cigarettes.(2)</p>	

References:

1. ASH. Use of electronic cigarettes among young people in Great Britain. 2020.
2. Hallingberg B, Maynard OM, Bauld L, Brown R, Gray L, Lowthian E, MacKintosh AM, Moore L, Munafo MR, Moore G. (2019) Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England, Scotland and Wales. <https://www.ncbi.nlm.nih.gov/pubmed/30936390>

326	Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.6 Role in the initiation of smoking (particularly focusing on young people)	P 62/ P 67/ P 69/ L 34 – 441	L L	48 26	Please see reply to comment 331.
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Role_in_the_initiation_of_smoking__particu

327	Froguel Alizee, Cancer Research UK, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	Flavours	(p64-65):	See Table 1, answers 1 and 7.
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This report concludes that flavours have a relevant contribution for attractiveness of use of e-cigarettes and initiation and cites a recommendation for flavours to be banned. However, Cancer Research believes more evidence is needed to understand to what extent flavours may help smokers to switch to vaping, as well as whether they might appeal to non-smokers and youth.

There is currently limited evidence on the role of e-cigarette flavours in both smoking cessation and youth use and further research is warranted before making any recommendation to restrict flavours but at this time, we do not believe there is sufficient evidence to justify a restriction. A recent Cancer Research UK rapid review of e-cigarette flavours and smoking cessation highlighted the limited evidence on this topic. Overall, there is some evidence that flavours play a role in promoting the appeal of e-cigarettes to adult smokers, but their role in smoking cessation is less clear.(1) Researchers at the University of East Anglia are currently undertaking a similar review on their role in youth use, due for publication later this year. In order to gauge the full impact that e-liquid flavours restrictions would have, it is imperative that more high-quality research is conducted to determine the balance of

potential benefits and risks of e-cigarette flavours in cessation and youth uptake.

As the Committee's report states (p65, 127-28), most consumers prefer flavours, including those who smoke. In Great Britain – where over half (59%) of adult vapers are ex-smokers (vs 2.9% never smokers) – only 2% of vapers use non-flavoured e-liquids.(2) In 2019, Action on Smoking and Health (ASH) asked e-cigarette users what they would do if flavours were no longer available.(2) The most popular response was still trying to get flavours, followed by using unflavoured products. However, concerningly around 1 in 5 respondents said they would smoke more /revert to smoking and around 1 in 10 said they would make their own e-liquid.

Furthermore, the report argues that an alternative to banning all flavours would be to regulate the ones that are “specifically attractive to young people” (p 65, 140-41). However, Cancer Research UK are not adequately convinced this distinction could be made and support further research to understand whether flavours perceived to be marketed primarily to youth, such as candy flavours, influence vaping uptake. This report states that “smokers like tobacco flavour the most” (p65, 18-9). This is not supported by a new study of 1,603 vapers (current smokers and ex-smokers who vape) in Canada and the US where almost two-thirds used a non-tobacco flavour.(3) Also in Great Britain more ex-smokers who currently vape prefer fruit flavours (34%) followed by menthol (25%) and tobacco (24%).(2)

Cancer Research UK do not believe there is currently sufficient evidence to conclude that e-cigarette flavours are promoting youth uptake, nor are they acting as a gateway to smoking. Thus, we believe there are limited grounds to justify restricting all e-cigarette liquid flavours. Further research is needed to determine whether flavours play a role in promoting smoking cessation.

References:

1. Davies A, et al. (Unpublished 2020). The role of e-cigarette flavours in product appeal and smoking cessation among adults: findings from a rapid review of the literature. See attachments.

2. ASH (2020). Use of electronic cigarettes among adults in Great Britain.
 3. Gravely, et al (2020) The association of e-cigarette flavors with satisfaction, enjoyment and trying to quit or stay abstinent from smoking among regular adult vapers from Canada and the United States: Findings from the 2018 ITC Four Country smoking and vaping survey.



Rapid_review_The_role_of_e-cigarette_flav

328	Froguel Alizee, Cancer Research UK, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	On nicotine (p66-67) Cancer Research UK believes that e-cigarettes should never be used by people who do not smoke, and young people in particular, as their long-term impact is unknown. However, the evidence so far indicates that using e-cigarettes are less harmful than smoking and can be an effective cessation tool. For people who do smoke – and therefore who are already addicted to nicotine – they can represent an opportunity for harm reduction.	See Table 1, answer 1.
329	Froguel Alizee, Cancer Research UK, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>On e-cigarettes potentially acting as a gateway to smoking and/or and renormalising smoking (p67-69):</p> <p>Based on the evidence available, Cancer Research UK conclude that there is insufficient evidence that e-cigarettes act as a gateway to smoking for young people.</p> <p>Research on the gateway effect is also often limited by the difficulty in accounting for common risk factors which may make young people more likely to smoke and vape, meaning the relationship between the two isn't necessarily causal. Whilst many studies attempt to control for this in their analysis, residual confounding often exists.</p> <p>As this report acknowledges (p68, 147-55), most of the research demonstrating a gateway effect of e-cigarette use to smoking comes from analysis of US data which isn't necessarily relevant to other nations with different regulatory environments and should therefore not be used to represent patterns of use elsewhere. In addition, US surveys define “current e-cigarette use” as “use on at least one day in the past 30 days”, definitions that fail to distinguish between experimentation and regular use. These broad definitions mean we are unable to ascertain whether the increase in e-cigarette use in</p>	Please see Table 1, answer 5.

young people is due to an increasing number of young people experimenting with these products or whether more people are using them regularly.

Much of the research examining the gateway effect which informed the Committee's preliminary opinion is relatively old (pre-2017). Given e-cigarette research is a fast-moving field, it is important that the Committee consider more recent evidence before drawing conclusions as to whether e-cigarettes are acting as a gateway to smoking among young people.

There is little evidence that many children in Great Britain are using e-cigarettes. According to a 2019 survey, among children aged 11-18 who have never smoked, only 0.1% of children use an e-cigarette more than once a week and nobody surveyed reported daily use. This coincides with the continuing decline in youth smoking.(1) A 2019 study also found the acceptability of smoking among young people in Great Britain has fallen faster since the introduction of e-cigarettes.(2)

References:

1. ASH. Use of electronic cigarettes among young people in Great Britain. 2020.
2. Hallingberg B, Maynard OM, Bauld L, Brown R, Gray L, Lowthian E, MacKintosh AM, Moore L, Munafo MR, Moore G at al. (2019) Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England, Scotland and Wales. <https://www.ncbi.nlm.nih.gov/pubmed/30936390>

330 Proaño
Gómez
Isabel,Euro
pean
Federation
of Allergy
and
Airways
Diseases
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Associatio
ns,Belgium

6.6 Role in the
initiation of
smoking
(particularly
focusing on
young people)

One of the goals of the Tobacco Products Directive 2014/40/EU has been to reduce the consumption of smoking products in the general population, addressing specifically the commercialisation of tobacco among the younger generations.

Relevant surveys show a significant uptake of e-cigarette use amongst youth in some parts of the world . In Europe, the use among young populations has followed the trajectory of increased marketisation: a Eurobarometer survey showed that 1 in 4 young people have tried e-cigarettes at least once . Initiation to smoking through e-cigarettes increased in Europe between 2012 and 2014 (Filippidis, 2017) , prompting a broad discussion about the role of e-cigarettes as a gateway to smoking. However, e-cigarette use has been shown to increase the risk of smoking initiation of

Thank you for your comment.

conventional cigarettes (Manzoli, 2016).

In light of the above alarming findings, EFA believes that the commercialisation of e-cigarettes and other related smoking products should be regulated in the same, or stricter, way as the tobacco products covered in the current Directive. This would include prohibiting industry practices such as flavourings, and prohibiting marketing techniques such as device colouring to reduce the current trend where young people find e-cigarettes cool (Page 63, lines 33-43).

Finally, we consider that young people should be also asked about their knowledge of the health effects of e-cigarettes and not just about their opinion on these devices. We therefore invite the EU institutions to launch or finance research linking health literacy and smoking and tobacco products. In this like, we consider e-cigarettes should include package warnings on health effects, including an explicit mention to the risk of developing COPD and increasing symptoms of other respiratory diseases, such as allergy and asthma.

331 Cipria Boboi,Asociatia Industriei de Vaping (Vaping Industry Association),Romania

6.6 Role in the initiation of smoking (particularly focusing on young people)

Line # P 62/ L 48
A number of reviews are used to justify the conclusion that there is strong evidence for a gateway effect. The Committee accepts that much of the evidence is from the US, and therefore not directly applicable in the context of the European Union.

Please see table 1, answer 5.

However, the committee fails to consider smoking rates among young people in the United States. This is problematic given the stated objective of this section of the report: namely to ascertain whether e-cigarette use among young people is likely to lead to them taking up smoking. If e-cigarettes were providing a gateway to cigarettes, as the committee suggests is evidenced, then US government data would show greatly increased smoking rates in line with the growing popularity of e-cigarettes.

However, US data shows that smoking among young people has actually fallen sharply since e-cigarettes were introduced to the market. Data from the US CDC (https://www.cdc.gov/healthyyouth/data/yrbs/pdf/trends/2015_us_

tobacco_trend_yrbs.pdf) shows that from 2013-2015 (during the period where e-cigarettes became popular) experimentation with cigarettes fell from 41.1% to 32.3%, and regular smoking fell from 5.6% to 3.4%. The data from 2019 showed that these numbers remained stable - with 32% having experimented with smoking. If e-cigarettes are a gateway to cigarette smoking in the US, then why is youth smoking falling so significantly there?

P 67/ L 26
While the studies noted in this section tend to find that those young people who use e-cigarettes are also likely to use cigarettes at some point, none consider why this might be, simply assuming that if both are used by the same subject then one led to the other. Recent evidence from the US - where the majority of the studies SCHEER has reviewed originate - indicates that the relationship might not be so straightforward in its causality.

Selya et al (2020) (<https://academic.oup.com/ntr/article-abstract/22/7/1123/5570011>), attached, undertook a secondary review of the “monitoring the Future” dataset, encompassing 12,421 8th and 10th-grade students. The analysis found that e-cigarette use “does not appear to be associated with current, continued smoking...failing to support claims that e-cigarettes have a causal effect on concurrent conventional smoking among youth”.

This study was published after the report from the committee was put to consultation; and given its highly authoritative source of data, It would be appropriate for the Committee to reconsider its conclusions in light of this new evidence.

P 69/ L 34 - 441
As the report notes, the Eurobarometer data looks at experimentation with e-cigarettes among those aged 15-24, which is an odd age range to review. In the majority of EU Member States, the legal smoking age is 18, meaning that 70% of the ages contained in the sample can legally smoke.

Since only 3% of those surveyed in Eurobarometer never smoked before using an e-cigarette, the report should consider the

possibility that the majority of those in the 15-24 age group who have tried e-cigarettes are doing so for the right reason: as legal age smokers looking for a less harmful alternative to smoking.

n/a

National data from Member States and other countries where TPD is in force can also be used to consider relevant trends. Irish Government data from 2019 (<https://assets.gov.ie/41141/e5d6fea3a59a4720b081893e11fe299e.pdf>) show smoking rates in the country have fallen from 23% in 2015 to 17% in 2019; concurrent with a rise in e-cigarette use from 3-5%. Less than 1% of non-smokers use e-cigarettes, according to the data.

332 Gnesutta Roberto, pri vato, Italy 6.6 Role in the initiation of smoking (particularly focusing on young people) 64 line 34 - 66 line 2 See Table 1, answers 7 and 1.

Nicotine without smoke: Tobacco harm reduction Royal College of Physicians. "However if [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance rights is difficult." From section 10.12 page 187

333 Novo Salvatore, University of Palermo, Italy, Italy 6.6 Role in the initiation of smoking (particularly focusing on young people) Page 2 lines 50-51 Please see table 1 answer 6

SCHEER preliminary opinion is highlighting the supposed weak evidence supporting the use of e-cig as an aid to quit smoking. Instead, there is at least a definitive RCT showing, in 866 participants, that e-cig are 2 times more effective than NRT in maintaining cessation from conventional cigarettes after 1 year (e-cig: 18%; NRT: 9,9%; ARR 1.75) (Haiek P et al. 2019). The evidence of the effectiveness on e-cig in smoking cessation was confirmed also in several and recently published meta-analyses, including one by the Cochrane Library database. 50 studies (26 RCTs) were reviewed, including a total of 12.430 participants. Such analysis showed the presence of an evidence from grade moderate to certain on the effectiveness of e-cig vs NRT in warranting a higher rate of cessation (risk ratio (RR) 1.69, 95% CI from 1.25 to 2.27; I2=0%). In absolute terms this translates into 4 successful cessations on 100 attempts (CI 95% from 2 to 8).

Page 52 lines: 13-49

The SCHEER opinion just focuses on the enhanced attractiveness for youth and potential gateway effect which is not supported by available evidence from the EU instead of highlighting the role of e-liquid flavors in switching adult smokers to a less harmful device. RIVM publication (Romijnders 2019) showed that among subjects who reported to never have smoked and never have used an e-cigarette the majority (68%) of the participants were not interested in trying a flavored e-cigarette.

In France, data from Chyderiotis (2020) show that adolescents who have used e-cigs are less likely to later transition to daily smoking than those who have not.

According to the latest 2020 report by the German Cancer Research Center (DKFZ), there is little evidence for a gateway effect on a population level. A reference to this German report should be added at page 68.

Several studies conclude that non-tobacco flavors and non-menthol flavors, especially fruit flavors, facilitate the switching of smokers compared to traditional tobacco and menthol flavors, see also attached papers. These evidences should be reflected in the final opinion of the SCHEER.



ref-333.docx

See Table 1, answers 7 and 1.

On the other hand, 32% expresses interest in trying a flavour, which is concerning, even if the majority is not interested. The majority of the people is also not interested in trying cigarette smoking, but it is still very problematic that many of them do.

334 Arnott Deborah, Action on Smoking and Health (UK), United Kingdom

6.6 Role in the initiation of smoking (particularly focusing on young people)

SCHEER concludes that there is strong evidence that e-cigarettes are a gateway to smoking for young people. This implies a causal link which is not substantiated by the evidence cited in the Opinion which fails to account sufficiently for common liability between smoking and e-cigarettes. More recent evidence further undermines the SCHEER conclusion. Analysis of the National Youth Tobacco Survey (2014–2017) found that less than 1% of US adolescents who use e-cigarettes first were established cigarette smokers. They were less likely to be smokers than adolescents who tried other combustible or non-combustible tobacco products first and propensity score matched

Please see table 1, answer 5.

adolescents without initial e-cigarette use. Shahab et al (2020) <https://tobaccocontrol.bmj.com/content/early/2020/02/19/tobaccocontrol-2019-055283>

The data for 2018 and 2019 further supported this analysis, showing that, for the great majority of those with any substantial cigarette smoking history, cigarettes were the first tobacco product tried, prior to any use of e-cigarettes. At the population level, therefore, the NYTS fails to give evidence of e-cigarettes acting as a gateway to smoking in adolescents. Rather it seems that e-cigarettes may be displacing cigarettes and becoming the preferred nicotine product. SCHEER also concludes that there is strong evidence that nicotine in e-liquids is implicated in the development of addiction. This is not supported by an analysis of US youth data, even though there is no limit on the nicotine strength of e-cigarettes unlike in the EU. An analysis of NYTS data for 2019, found little evidence of substantial nicotine addiction attributable to the use of e-cigarettes. Among all students who were past-30-day-cigarette users but had never tried any other tobacco product, responses consistently pointed to minimal dependence with only 8.7% reporting any craving for tobacco products, and 2.9% reporting wanting to use within 30 minutes of waking. Over 46% reported using an e-cigarette on 10 or fewer days in their lifetime. Only 2.1% were classified as frequent users of e-cigarettes on 20 or more days in the past month. This contrasted markedly with students who had smoked more than 100 cigarettes (so meeting the US definition for regular cigarette smoking), where 65.0% reported craving, 48.7% wanted to use within 30 minutes of waking, and 66.1% used e-cigarettes on 20 or more days in the past month. This group had mostly started their tobacco careers with cigarettes, and their pattern of dependence typifies that attributable to cigarette use. Jarvis et al (2020) <https://www.queios.com/read/745076.5>

335 Salzer Mario, Interest Group Ex-Smokers (87705313 6906- 6.6 Role in the initiation of smoking (particularly focusing on young people)

Page 62, Line 1-2
 In the US, they have become the most common tobacco products used by youth, driven in large part by marketing and advertising by electronic cigarette companies (Fadus, et al. 2019, Walley, et al. 2019).
 This assessment omits some context. It's not just commercial ads

Please see table 1, answer 5.

	06),Germany		<p>which have driven youth consumption up. Anti-vaping campaigns have more so contributed to the awareness and use prevalence among US teenagers. [Minton 2020] points out that teen uptake has been stoked by ill-conceived messaging and scaremongering campaigns. Most notably the TV and internet advertisements with *SCIENCE-FICTION WORMS EATING BRAINS* cannot have possibly deterred youths. Given adolescents typical reaction to such blatant misrepresentations, it's more probable this has contributed more to the uptake than any of the commercial vaping/tobacco companies did.</p> <p>In particular since the anti-vaping campaigns matched the commercial spending, and more *factually* targetted teen demographics.</p> <p>As commercial advertisements for tobacco/vaping products are widely banned within the EU (except for e.g. Germany still), the pitfalls of similar hyperbole campaigns (as in e.g. Spain) seem significantly more realistic and noteworthy for a scientific assessment.</p> <p>Ref: Minton (2020). How Anti-Vaping Campaigners Helped Create the Youth Vaping "Epidemic"</p>	
336	Salzer Mario, IG-XR (87705313 6906-06), Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>Page 65 – Line 55-56</p> <p>(1) that flavours should be prohibited, mainly because they are likely to attract children and young people ... There's a distinctive assumption throughout the report that flavours were the primary driver behind teen use of e-cigarettes, yet very little consideration on what the potential consequences of a flavour prohibition would be. (Even if such a ban was indeed targeting just accessibility for teenagers.) Given the recurring citations of the situation in US, it's unclear why none of the outcomes found any mention. There have been localized flavour bans in some states and cities. And smoking relapse doesn't seem constrained to adults in some of the early reports. see [Yong Yang, Eric N. Lindblom, Ramzi G. Salloum, and Kenneth D. Warda 2020]:</p> <p>> These findings suggest that comprehensive local flavor bans, by themselves, cannot sharply reduce the availability or use of</p>	Please see table 1, answers 1 and 7. Furthermore, it is too soon to evaluate on the impact of the flavour ban in Finland.

flavored tobacco products among residents. Nevertheless, local bans can still significantly reduce overall e-cigarette use and cigar smoking but *may increase cigarette smoking*. The outcomes may well divert for the EU context, since teen use is less prevalent in most member states, and migration onto Cannabis vaporizers is less probable. It would be apt nonetheless to yield some consideration to the gateway probability of artificial tobacco flavourings. (Poorly resemble the taste of ash/cigarettes, yet close enough for reaccustomization and on-ramp effects.) Similar flavour bans have been tried in Finland, btw. The SCHEER report ought to include the effects on smoking prevalence there, and why the ban has been revoked henceforth. The ban experiment as planned in Denmark and the Netherlands would best be observed in a followup report.

Ref:

Yang et al (2020). The impact of a comprehensive tobacco product flavour ban in San Francisco among young adults. <https://doi.org/10.1016/j.abrep.2020.100273>

337	Schmidt Norbert, Intereessenge meinschaft E-Dampfen e.V. (IG-ED), Germany	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>P 63 L 4-7</p> <p>Quote from the uploaded study: "Electronic cigarettes may have offset conventional smoking among US adolescents between 2010 and 2018 by maintaining the total nicotine use prevalence and diverting them from more harmful conventional smoking. Additionally, electronic cigarette users appear to initiate at older ages relative to conventional smokers, which is associated with lower risk."</p> <p>Ref: Kozlowski (2017) Adolescents and e-cigarettes: Objects of concern may appear larger than they are? Foxon et al (2020). Electronic cigarettes, nicotine use trends and use initiation ages among US adolescents from 1999 to 2018. https://doi.org/10.1111/add.15099</p>	Thank you for your comment.
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338	Kuttruf Andrej, Eva po, United Kingdom	6.6 Role in the initiation of smoking (particularly focusing on young people)	<p>'Only 0.8% of people who have never smoked reported that they currently vape', UK https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#the-use-of-electronic-cigarettes-e-cigarettes-great-britain</p>	See Table 1, answer 1.
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The statistical evidence is clear that there is no significant uptake of vaping among non-smokers. However what statistics also show is a clear reduction in teen smoking and in overall smoking rates in countries where vaping is more widely adopted among smokers as

in the UK (see statistics above).

The studies quoted in the US omit, that the US market is an unregulated market (opposed to the European market) and has no nicotine restriction. Even so the studies mentioned in the US are misleading, as it doesn't look at regular use and only measures experimental use (tried once a month vs regular use). Regular use of e-cigarettes is low even in the US, which has one of the highest rates of youth vaping. The UK, EU countries and other regulated markets have all seen only minimal uptake of teen vaping. (See statistics referenced above).

Either way, the risk of teen vaping uptake has to be measured against the potential public health prize of switching adults smokers to a far less harmful alternative and saving 700 000 deaths every year in the EU caused by smoking.

However, if [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer-friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult. <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction>, (Section 12.10 page 187).

339	Cavina Stefania, Smoky, Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Abstract 49-51 Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping”.	Please see table 1, answer 6.
340	Spina Francesco, private, Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Page 71 lines 30 to 34. Attached the statistics from which you can assess the high smoke cessation rate using electronic cigarettes. those statistics are highly valuable to determine that flavoured liquids and e-cigarette are a valid alternative to tobacco smoke cessation and lung cancer reduction.	There was no attachment linked to this comment.

341	Albrecht Hans-Peter, Interessengemeinschaft Elektronisches Dampfen (IG-ED), Germany	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	p.70 There is considerable evidence that quitting combustible tobacco with the help of vaping is twice as effective than by NRT only. Also there are a big number of successful quit stories through vaping. Although conferred to as „anecdotal“, the more there are, the more they become scientifically/evidentially relevant (see Carl Phillips: https://antithrlies.com/2015/01/09/science-lesson-on-anecdotes/).	11.47-48_ Thank you for your comment.
342	Brown Jamie, University College London, United Kingdom	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	p.70, line 31, includes the description ‘During this timeframe, experimentation with the use of 31 electronic cigarettes for smoking cessation increased (3.7% to 9.7%), while on the contrary 32 the use of pharmacotherapy (14.6% to 11.1%) and smoking cessation services (7.5% to 33 5.0%) declined across the EU (Filippidis, et al.,2019)’. Please note we have assessed this association formally (albeit in UK only rather than in EU) with time-series analyses: https://www.bmj.com/content/354/bmj.i4645 . This paper is published in The BMJ and has been widely cited (130 times in Scopus).	Thank you for your comment
343	Mastandrea Aldo, Starman, Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	La Sigaretta elettronica ad oggi è il miglior metodo per la cessazione alla dipendenza dal Fumo! È l'unica possibilità per l'abbassamento della nicotina assunta e che non ha effetti collaterali! Sono 7 anni che uso sigarette elettroniche e cessato totalmente con le sigarette tradizionali! Dopo aver provato tutte le possibili strade per la cessazione del fumo, l'unica ad aver reso possibile tutto ciò è stata la Sigaretta Elettronica! In 7 anni I benefici sono diversi, dalla salute ai benefici fisici di tutti i giorni! Io chiedo che venga sponsorizzata e pubblicizzata dalla comunità europea e da tutti gli stati membri!	Thank you for your comment.
344	Kröger Knut, Helios Klinik Krefeld, Germany	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Page 71; lines 19 - 28 and lines 33 – 34 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use Taking the above RCTs into account and the information available through systematic reviews that have synthesized the observational literature on the impact of electronic cigarette use the most recent 2020 Surgeon general’s report on Smoking Cessation (Surgeon General 2020) concluded that “The evidence is inadequate to infer that e-cigarettes, in general, increase	Please see table 1 answers 5 and 6.

smoking cessation”. Moreover the report also concluded that “the evidence is suggestive but not sufficient to infer that the use of e-cigarettes containing nicotine is associated with increased smoking cessation compared with the use of e- cigarettes not containing nicotine, and the evidence is suggestive but not sufficient to infer that more frequent use of e-cigarettes is associated with increased smoking cessation compared with less frequent use of e-cigarettes.”

Comment: It is interesting that SCHEER Preliminary Opinion on Electronic cigarettes paper again just quote others without going into detail. The 2020 Surgeon general’s report on Smoking Cessation also concluded: Point 8: “The evidence is suggestive but not sufficient to infer that pre-loading (e.g., initiating cessation medication in advance of a quit attempt), especially with the nicotine patch, can increase smoking cessation.”

Point 12: “The evidence is suggestive but not sufficient to infer that fully and consistently integrating standardized, evidence-based smoking cessation interventions into lung cancer screening increases smoking cessation while avoiding potential adverse effects of this screening on cessation outcomes.”

Thus, we have a general problem with sufficient evidence in a lot of strategies of smoking cessation which are accepted for much longer time. The SCHEER Preliminary Opinion on Electronic cigarettes paper ignores more recent evidence that showed that electronic cigarettes are successful in helping smokers to quit smoking. Studies by Lucchiari (2020) and Glasser (2020) demonstrated that more frequent and stable use of electronic cigarettes can help smokers to quit smoking. O’Leary et al stated already in 2017: “Based on our systematic reviews of literature published up to April 2016, we conclude [...] Overall, there is encouraging evidence that vapour devices can be at least as effective as other nicotine replacements as aids to help tobacco smokers quit.”

References

O’Leary et al (Canada, 2017) Clearing the Air: A systematic review on the harms and benefits of e-cigarettes and vapour devices <http://helveticvape.ch/WP/wp-content/uploads/2017/01/report-clearing-the-air-review-exec-summary.pdf>

Lucchiari 2020 Benefits of e-cigarettes in smoking reduction and in pulmonary health among chronic smokers undergoing a lung cancer screening program at 6 months.

Glasser, A., et al. (2020). "Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in

the Population Assessment of Tobacco and Health (PATH) Study." Nicotine & Tobacco Research.

Finally, the chapter concluded: There is a lack of robust longitudinal data on the effect of electronic cigarettes on smoking cessation.

Comment: The phrase "robust longitudinal data" is not used in the 2020 Surgeon general's report on Smoking Cessation at all. Thus, in the context with e-cigarette und tobacco heating systems the SCHEER Preliminary Opinion on Electronic cigarettes paper ask for something which is not available for any smoking cessation strategy.

I as a physician specialised in vascular medicine need simple and effective tools that are accepted by a the majority of smokers. E-cigarette und tobacco heating systems are helpful in my daily life. There is no point in setting the bar so high that no product or strategy reaches this level of evidence.

345	Sweeney Damian, NNA Ireland ,Ireland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>On page 70 lines 27 to 55 the SCHEER opinion discusses population experimentation and usage of e-cigarettes, but fails to mention the effects this has had on smoking prevalence at a population level. This is a vital piece of information to assess the role of e-cigarettes in cessation. Data from national surveys, Ireland in this case, provide conclusive proof that e-cigarettes have contributed significantly to a substantial reduction in smoking prevalence since 2015-16. Smoking prevalence was 23% in 2015 and 2016. In the following 3 years smoking prevalence fell to 17%, this coincided with a rise in e-cigarette use from 3% to 5%. The Healthy Ireland surveys, commissioned by the Health Service Executive, gave a breakdown of methods used by successful quitters. In 2017, 37% of those who had successful quit smoking used e-cigarettes, compared to 18% who used pharmacotherapy (Healthy Ireland 2017, page 17). In 2018 the number that used e-cigarettes in a successful quit attempt rose to 41%, those using pharmacotherapy fell to 17% (Healthy Ireland 2018, pages 8 & 9). And in 2019, 38% of those who made a quit attempt used e-cigarettes and only 7% of those who made a quit attempt did so on the advice of a health professional (Healthy Ireland 2019, pages 3 & 4). It's important to note that e-cigarettes use among non-smokers in Ireland has been consistently 1% or less. A pilot study in England examining the use of e-cigarettes for smoking cessation, conducted by Coffey et al (2020), found that 62% of those engaged with the study at 4 weeks were smoking</p>	Please see table 1 answer 1.
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abstinent.
 Population data from the USA found that “The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level (Zhu S-H et al, 2018)”
 Simply referencing the prevalence of e-cigarette use offers no real would guidance to regulators, if it is not compared to the effects this has on smoking prevalence at a population level. As a disruptive technology, e-cigarettes are displacing smoking and driving down smoking prevalence at an accelerated rate. This information needs to be seriously considered.

Ref.:
 Coffey (2020) Using e-cigarettes for smoking cessation: evaluation of a pilot project in the North west of England.
 Zhu (2017) E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys

346	Sweeney Damian,N NA Ireland ,Ireland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Page 71 lines 1-34</p> <p>Two randomised control trials are cited in this section of the opinion, Hajek, et al (2019) and Walker et al (2020), both of these studies show e-cigarettes to be significantly more effective than NRT’s. In the case of Hajek et al, e-cigarettes were 83% more effective than NRT’s, and Walker et al found that e-cigarettes combined with NRT’s to be 2.5 times more effective than patches alone. The most recent Cochrane review, published on the 14th October, also found e-cigarettes to be significantly more effective than NRT’s, 67% more effective (Hartmann-Boyce et al., 2020). In their study: Moderators of real-world effectiveness of smoking cessation aids: a population study, Jackson et al (2019) conclude that “Use of e-cigarettes and varenicline are associated with higher abstinence rates following a quit attempt in England”. The SCHEER opinion has concluded the opposite of what the cited studies actually found.</p>
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Please see table 1, answer 6.

It must also be noted that the USA does not have the same regulatory framework in place for e-cigarettes as the EU, meaning a lot of products available in the USA are not available in the EU. The SCHEER opinion states in their terms of reference, page 10 lines 7-9, “The assessment should include and address the role of e-cigarettes, looking into potential impacts on the EU context”. As

such, USA data relating to products not available in the EU has little relevance in the EU context.

347	Ollila Eeva, Cancer Society of Finland, Finland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>As e-cigarettes are often used together with conventional tobacco products, it would have been good to include more profound assessment of the impacts of concomitant use, as there are some indications that dual use may be markedly more harmful than use of either type of the product alone (Talal et al 2018).</p> <p>Talal Alzahrani, Ivan Pena, Nardos Temesgen, Stanton A. Glantz. Association Between Electronic Cigarette Use and Myocardial Infarction. Am J Prev Med 2018; Published online ahead of print 22-AUG-2018 DOI information: 10.1016/j.amepre.2018.05.004</p>	<p>Please see table 1 answer 1. Dual use is addressed in the opinion.</p>
348	Gorini Giuseppe, Oncologic network, prevention and research Institute (ISPRO), Florence, Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>At the end of the paragraph 6.7, I would add some sentences on the issue of smoking reduction and dual use: “Is there health benefit of smoking reduction or dual use of tobacco cigarettes and electronic cigarettes, even with a significant reduction in tobacco cigarette consumption? In a Danish cohort of about 20,000 subjects, heavy smokers (≥ 15 sig/die) who 30 years earlier had reduced their cigarette consumption by an average of 62%, recorded a risk decrease in developing lung cancer of 27% only, compared to heavy smokers who hadn't changed their consumption. In contrast, light smokers (< 15 sig/die), those who had quit for < 10 years (i.e. recent quitters), those who had quit for > 10 years and never smokers, reported a 56%, 50%, 83%, and 91% risk reduction, respectively [1,2]. Thus, in heavy smokers who reduced consumption by at least 50% without quitting (reducers), the risk reduction was disproportionately smaller, about half (25%). This discrepancy was largely attributable to compensatory mechanisms that smokers implement to obtain more nicotine when they smoke fewer cigarettes. Furthermore, reducers did not reduce the risk of developing myocardial infarction at all, whereas quitters benefited of a 30% reduction [3]. Reducers did not register any reduction in hospitalizations for emphysema or chronic bronchitis, while those who quit recorded a 43% reduction in hospitalization rates for chronic obstructive bronchial pulmonary diseases [4]. Finally, in reducers the risks of dying from all causes, cardiovascular diseases, smoking-related cancers, and respiratory diseases did not change. On the other hand, those who succeeded in quitting, reduced the risk of dying from all causes by 35%, and of dying from smoking-</p>	<p>Please see table 1 answer 1. Dual use is addressed in the Opinion.</p>

related cancers by 64% [5]. In another cohort study, around 42,000 Norwegians were analyzed for cardiovascular risk factors at the age of 35-49, and were followed from the mid-1970s through 2002, to evaluate their causes of death. Relative risks adjusted for the most important cardiovascular risk factors showed that even smoking 1-4 cig/die only determined a threefold risk of dying from ischemic heart disease compared to never smokers; a threefold risk for men and a 5 times higher risk for women of dying from lung cancer. On the other hand, for those who smoke >25 sig/die, the risk of dying from lung cancer was 36 times higher in males and 32 times higher in women, while the risk of dying from heart attack was about 4 times higher than that recorded in never smokers for both men and women [6]. The marked difference between the observed decline in the probability of dying from lung cancer among heavy smokers and smokers of <5 cig/die (from 36 to 3 in men; from 32 to 5 in women), compared to the much less net decrease in the risk of dying from ischemic heart disease among heavy and very light smokers (from 4 to 3 in both sexes) is related to the different pathogenetic mechanisms of smoking in the onset of the two diseases. Thus, in smokers of <5 cig/die the risk of dying from myocardial infarction remained high, while the risk of dying from lung cancer was significantly lowered, even though not cancelled.

In conclusion, smoking reduction does not seem an efficient and effective strategy to reduce the risk of smoking-related diseases. Among dual users of tobacco cigarettes and electronic cigarettes, the best strategy to recommend is to stop dual use, and to exclusively use electronic cigarettes.”

References

1. <https://pubmed.ncbi.nlm.nih.gov/17558820/>
2. <https://pubmed.ncbi.nlm.nih.gov/16189363/>
3. <https://pubmed.ncbi.nlm.nih.gov/12775785/>
4. <https://pubmed.ncbi.nlm.nih.gov/12403880/>
5. <https://pubmed.ncbi.nlm.nih.gov/12446255/>
6. <https://pubmed.ncbi.nlm.nih.gov/16183982/>

349	Landl Michael,W orld Vapers'	6.7 Role of electronic cigarettes in the cessation of	Page 71, Lines 19-27: The preliminary report’s literature review does not take into account any literature, of which there is plenty, that supports e-cigarettes as smoking cessation. But, an evidence review from Public Health England [1][2][3] found that “e-	Please see table 1, answer 2. The opinion has been updated and additional references are added where needed.
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cigarettes could be contributing to at least 20,000 successful new quits per year and possibly many more, e-cigarette use is associated with improved quit success rates over the last year and an accelerated drop in smoking rates across the country, many thousands of smokers incorrectly believe that vaping is as harmful as smoking; around 40% of smokers have not even tried an e-cigarette.

Also, the French Federation on Addiction (FFA) published an official report [4] recognising that e-cigarettes are “a complementary tool in reducing risks which has enabled a large number of smokers to significantly reduce the negative effects of tobacco”.

Another systematic review and meta-analyses [5] assessed the findings of six studies, involving 7,551 participants, which reported smoking cessation after using e-cigarettes found that the use of e-cigarettes is associated with smoking cessation and reduction.

To add to this point, a Cancer Research UK-funded study by University College London, UK found that vapour products users are 95% more likely to be successful at quitting smoking than those who do not use vapour products. [6]

On robust longitudinal data on cessation, there are studies to that effect, that the European Heart Network has not taken into account. According to a longitudinal study [7] assessing the behaviour of 844 e-cigarette users over 12 months, the conclusion was that “E-cigarettes may contribute to relapse prevention in former smokers and smoking cessation in current smokers.”

Page 71: Lines 30-34: See previous remarks about the evidence that finds e-cigarettes an effective secession method for smokers.

References:

- [1] [2] [3]
Ann McNeill, Leonie S Brose, Robert Calder, Linda Bauld, Debbie Robson,
Evidence review of e-cigarettes and heated tobacco products 2018, A report
commissioned by Public Health England
[4] Federation Francaise d’Addictologie, Rapport D’Orentation et recommandations

			de la commission d'audition [5] Muhammad Aziz Rahman ,Nicholas Hann,Andrew Wilson,George Mnatzaganian,Linda Worrall-Carter, E-Cigarettes and Smoking Cessation: Evidence from a Systematic Review and Meta-Analysis [6] Jackson SE, Kotz D, West R, Brown J. Moderators of real-world effectiveness of smoking cessation aids: a population study. <i>Addiction</i> . 2019 Sep; [7] Jean-François Etter, Chris Bullen, A longitudinal study of electronic cigarette users	
350	Martinez Javier,JT Internation al SA,Switzer land	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	P.70, 1.19-28 Please revise the statement “Taking into account data from cohort studies and randomised control trials, the weight of evidence for smoking cessation is weak...” Based on the scientific literature available, the evidence should not be qualified and reported as “weak”. The most recent Cochrane Review document contradicts SCHEER conclusion, pointing out, “we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT.” See Hartmann-Boyce et al. 2020. The review concludes, “Nicotine e-cigarettes probably do help people to stop smoking for at least six months” adding, “None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use.” SCHEER downplays the abundance of data showing that in countries where vaping is more prevalent, smoking rates have declined while vaping has increased. SCHEER fails to comment on the findings of the 2018 review conducted by the UK Royal College of Physicians and Public Health England, noting “the evidence suggests that e-cigarettes have contributed tens of thousands of additional quitters in England.” SCHEER fails to refer to observational studies that provide further insight into whether the effects observed in randomized controlled trials are observed in the real world. Glasser et al. 2017 and Villanti et al. 2018 found that vaping facilitates quit attempts and increases cessation, supporting the notion of a likely effectiveness of e-cigarettes. Population studies in the US and the UK have also found that smokers who use e-cigarettes to quit have significantly higher quit rates than those who do not, highlighting the notion that quit attempts and quit rates have been increasing since vaping became popular. (Zhu 2017, Johnson 2019, Jackson et al. 2019, Beard et al. 2016). A systematic review and meta-analysis from Austrian researchers point towards a potential for e-cigarettes as a smoking cessation tool. (Grabovac et al. 2020) A recent US study authored by Glasser et al. (2020) indicates that consistent and	Please see table 1 answer 6

frequent e-cigarette use over time is associated with cigarette smoking cessation among adult smokers. These results underscore the importance of carefully defining and characterizing e-cigarette exposure patterns, potential confounders, and use of e-cigarettes to quit smoking, as well as variations in length of the smoking cessation. Observational studies should account for the frequency of e-cigarette use when evaluating the association between e-cigarette use and cigarette smoking abstinence.” SCHEER notes, “There are currently four generations of electronic cigarettes in the EU market, but this evolves in a very rapid way and other products, already marketed in the USA, are expected to come soon.” Studies available based on the use of first- or second-generation devices, which while still available on the market, are not representative of the more efficient third and fourth generation devices which are more often used. The wide variation in nicotine absorption from different e-cigarette devices should be considered in studies of e-cigarettes for smoking cessation. SCHEER fails to consider this information in the context of an effective transition from smoking to e-cigarettes arising with advanced devices, ignoring the notion that more advanced e-cigarettes are more satisfying to consumers than first-generation devices and will thus play an increasing role in switching from smoking. While it is impossible to demonstrate that changes in population smoking can be attributed to e-cigarettes or any other intervention, it is noteworthy that the decline in smoking in both the USA and UK has accelerated over the period that vaping has become widespread and population quit rates have increased.



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351	Ross Louise, National Centre for Smoking Cessation and Training,	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	19-23 I speak from clinical experience, having seen, through my work in a Stop Smoking Service (SSS) and having gathered views from many peers in SSSs, that for those who thought they had tried everything, vaping worked where nothing else had come close. A key factor in success is the message that is attached to the behavioral support. If you tell smokers that vaping is potentially harmful, is no better than smoking, that the products aren't safe,	Thank you for your comment.
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United
Kingdom

they will carry on smoking. We know that half of smokers will die from a smoking-related disease, and die far too soon. For every person who dies of a smoking-related disease, another 20 will suffer years of disability and illness caused by their smoking. If you tell smokers, confidently, that vaping can help them stop smoking, they will try it, because smokers want a solution. They hope that this time the plan will work. With vaping, my team saw many successful quitters, even ones who hadn't intended to quit. They were the accidental quitters who started because their partner was trying it, and they thought - why not? I need also to mention pregnant smokers. We try so hard to get them to quit, for their sake and for the sake of their babies. We would never of course suggest that a non-smoking pregnant woman try a vape, but for those who were smoking, vaping is a much safer option, supplying them with the nicotine that they are used to without the deadly smoke. If they were smoking anyway, this harm reduction method must be considered. It's no good saying to a pregnant smoker that she has to quit with nicotine replacement therapy if that means that she never comes back to the service. Vaping keeps women coming back for more support, and we can then talk to them about maintaining a smokefree home and not starting to smoke again after the baby is born. The last group that I want to talk about is people with poor mental health. You will be very familiar with the statistics that tell the shocking story of early death and avoidable disease among this extremely disadvantaged group. As a clinical practitioner managing a service, I talked to many patients in a mental health facility. They were angry about the smokefree policy that didn't allow them to smoke on the wards. When I explained that we were planning that they could vape instead, they jumped at the chance. They had all tried nicotine replacement therapy before, and found it unsatisfactory. If we hadn't offered vaping, they would have continued smoking, in secret when they were in-patients, and freely on discharge. E-cigarettes gave them a step up to better health.

Please, when deliberating after you've read the submissions to this consultation, bear in mind that even if e-cigarettes were half as dangerous as smoked cigarettes, they would still save lives. We know they are safer than 50% compared with smoked cigarettes.

			Your committee title is about 'emerging risks'. Please don't make decisions that protect the ever-present longstanding risk - smoked tobacco.	
352	Poirson Philippe, Sovape, France	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>SCHEER opinion missed many serious observational studies and analyses in Europe on smoking cessation using vaping:</p> <ul style="list-style-type: none"> - The Cochrane review with a serious and rigorous work on 50 studies concluded, « There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT » - The E3 clinical trial led by Dr. Mark Eisenberg in Canada shows that "these findings show that nicotine e-cigarettes are effective for smoking cessation in the short term" during the American College of Cardiology Congress. - In France, in a context governed by TPD, more than 700,000 people have stopped smoking at long term thanks to vaping in 2017, according to the analysis of Santé Publique France. According to the same source, vaping is becoming last years the most common method used to quit smoking in France. - In the United Kingdom, vaping has resulted in a net increase in smoking cessation of at least 50,000 to 70,000 people per year, according to the analysis of Emma Beard et al. from the Smoking Toolkit Study data. - Analysis by Jackson et al (2019) shows that vaping and varenicline are associated with a higher abstinence rate in quit attempts in England. - The analysis of Farsalinos et al (2016) of the Eurobarometer 2014 data showed that at least 6 million Europeans had quit smoking with vaping. - Study from Van Gucht et al (2017) show in Belgium and Netherland, the vast majority of vape shop customers quit smoking and improve their health. - The pilot experiment in Salford (UK) obtained excellent results in helping people to stop smoking under real-life conditions. - The pilot experiment in Olten (CH) also obtained excellent results in helping people to stop smoking under real-life conditions. - Even in USA, analysis by Zhu et al. and thousands of testimonies from real people show vaping help to quit harmful cigarettes. The themes of conditions favourable to optimise the public health benefits of mass smoking cessation through the switch to vaping 	Please see Table 1, answer 6.

have not been addressed by SCHEER although they are essential to assess TPD and should have been the focus of a report evaluating the effects of regulation:

- The weight of misinformation campaigns against vape seems particularly deleterious, as the British and French health authorities point out (PHE 2018, Académie Nationale de Médecine 2019);
- The importance of flavours, availability and affordability of vape products in attracting smokers out of smoking (Farsalinos, Russell 2018, Friedmann 2020).

353	Gallus Silvano, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>It is important to notice that most dual users (i.e., users of conventional tobacco cigarettes and e-cigarettes) use e-cigarettes where smoking conventional cigarettes is prohibited. For example, in a study from Italy, among 395 e-cigarette users, 71.5% used e-cigarettes in at least 1 smoke-free indoor environment, 53.7% in workplaces, 49.5% in restaurants and bars, 33.5% in train/metro stations or airports, and 18.4% in public transports. (Gallus S, Borroni E, Liu X, et al. Electronic cigarette use among Italian smokers: patterns, settings, and adverse events. Tumori. 2020 Apr 26:300891620915784). E-cigarettes should be banned where conventional cigarettes are forbidden.</p> <p>Moreover, I concur with Giuseppe Gorini's comments: being the reduction in smoking intensity (in terms of cigarettes/day) an ineffective strategy to reduce the health risks associated to smoking, dual use should be discouraged also in case of substitution of conventional cigarettes with e-cigarettes.</p>	<p>Thank you for this information.</p> <p>Please see the reply to comment 348.</p>
354	No agreement to disclose personal data	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Page 70 L53: REAL-WORLD DATA AND THE SCIENTIFIC EVIDENCE SHOWS E-CIGARETTES ARE EFFECTIVE FOR CESSATION</p> <p>Randomised control clinical trials, observational studies and population data shows that when e-cigarettes are regulated proportionately, they have high rates of success in achieving smoking cessation compared to other alternatives. See Cochrane Review 2020[1], as highlighted in the Summary Section. In France, regular e-cigarette use is associated with a significantly higher decrease in the number of cigarettes smoked per day compared with daily smokers who do not vape, as well as a higher adjusted relative risk of smoking cessation[2]. In the UK, adult smokers who use e-</p>	<p>Please see table 1, answer 6.</p>

cigarettes to quit smoking are 60% more likely to succeed than those using traditional, over-the-counter NRT products or willpower alone [3] with e-cigarettes having helped an estimated 50,000 extra smokers per annum stop smoking each year who would otherwise have continued[4]. In New Zealand, e-cigarettes are the most commonly used aid to help quit or cut down tobacco smoking [5]. In the US, the increase in e-cigarette use by adult smokers has been shown to be associated with a statistically significant increase in smoking cessation rates at population level [6] with daily e-cigarette users 3 times more likely to quit smoking than smokers who never used e-cigarettes[7]. An analysis of the US Population Assessment of Tobacco and Health nationally representative survey has also showed that, for smoking cessation among current adult smokers at Wave 1, 17.3% had quit smoking at Wave 3 and smoking cessation was more likely amongst frequent vapers who used flavoured e-cigarettes compared to less frequent users or adult smokers who never used e-cigarettes[8].

Page 70 Line 19: DUAL USERS ARE MORE MOTIVATED TO STOP SMOKING, ARE LESS DEPENDENT ON COMBUSTIBLE CIGARETTES AND ARE MORE LIKELY TO USE E-CIGARETTES TO TRANSITION FOR COMPLETE SMOKING CESSATION

The Opinion omits that a growing body of scientific evidence shows dual users of both e-cigarettes and combustible tobacco have an increased likelihood of going on to replace smoking entirely [9]. Dual users are undergoing a longer-term, dynamic transition from smoking to non-smoking, with different users moving through different stages that are not made evident in snapshot surveys [10]. Further evidence also shows that in the UK, dual use of e-cigarettes is not associated with reduced overall quit rates compared with exclusive smoking or dual use of NRT with dual use of e-cigarettes being associated with a higher quit rate attempt [11]. In the US, dual users who smoked and used e-cigarettes were most likely to have completely quit smoking in subsequent years [12]. We respectfully suggest SCHEER also highlight to the readership in their final opinion that dual use of combustible cigarettes and NRT products

is a stated aim for these products in the EU, with a view to making smoking cessation easier[13].



6.7_Role_of_electronic_cigarettes_in_the_ce

355 Chaplia Maria,Consumer Choice Center,United States 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

PAGE 71, LINES 19-27: The claim that non-smokers would get introduced en masse to smoking due to vaping seems not to be supported by data from the newest Action on Smoking and Health (ASH) UK report. It states that “only 0.3% of never-smokers are current vapers (amounting to 2.9% of vapers), down from 0.8% in 2019”.

Please see reply to comment 349.

A study conducted by the University College London in 2019 analysed data from over 50,000 smokers from 2006 to 2017 and found that using e-cigarettes in order to quit was positively associated with the quit success rates, with every 1 per cent rise in use of e-cigs associated with a 0.06% increase in the quit success rate.

An evidence review from Public Health England found that “e-cigarettes could be contributing to at least 20,000 successful new quits per year and possibly many more, e-cigarette use is associated with improved quit success rates over the last year and an accelerated drop in smoking rates across the country, many thousands of smokers incorrectly believe that vaping is as harmful as smoking; around 40% of smokers have not even tried an e-cigarette.

Also, the French Federation on Addiction (FFA) published an official report recognising that e-cigarettes are “a complementary tool in reducing risks which has enabled a large number of smokers to significantly reduce the negative effects of tobacco”.

Another systematic review and meta-analyses assessed the findings of six studies, involving 7,551 participants, which reported smoking cessation after using e-cigarettes found that the use of e-cigarettes is associated with smoking cessation and reduction.

To add to this point, a Cancer Research UK-funded study by University College London, UK found that vapour products users are 95% more likely to be successful at quitting smoking than those who do not use vapour products.

On robust longitudinal data on cessation, there are studies to that effect, that the European Heart Network has not taken into account. According to a longitudinal study assessing the behaviour of 844 e-cigarette users over 12 months, the conclusion was that “E-cigarettes may contribute to relapse prevention in former smokers and smoking cessation in current smokers.”

PAGE 71: LINES 30-34: See previous sections for evidence on why e-cigarettes an effective cessation tool method for smokers.

Ref:

Etter (2014). A longitudinal study of electronic cigarette users.

McNeill (2018). Evidence review of e-cigarettes and heated tobacco products 2018

A report commissioned by Public Health England.

FFA (La Fédération Française d'Addictologie) (2016).

Rahman (2015). E-Cigarettes and Smoking Cessation: Evidence from a Systematic Review and Meta-Analysis.

Jackson (2019). Moderators of real-world effectiveness of smoking cessation aids: a population study.

356 O'Leary Renee, Center of Excellence of the Acceleration of Harm Reduction, University of Catania, Italy, Italy

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

P70 L37-41 An appreciable number of respondents in an EU survey report using ENDS in their quit attempt, averaging for the EU countries surveyed at just under one in five people who smoke. Country Used ENDS in quit attempt Germany 15.9%; Greece 28.7% Hungary 16.2%; Netherlands 43.8%; Poland 13.0%; Romania 11.0% Spain 5.0%; From Hummel et al., 2018 P71 L19-34 The recently published Cochrane review (Hartmann-Boyce et al., 2020) concludes there is moderate-certainty evidence that ENDS use for cessation results in a higher quit rate than NRT, RR 1.69 (CI 1.25-2.27). ENDS produced a higher quit rate than behavioural support only or no support, RR 2.50 (CI 1.24-5.04), although the evidence is of very low certainty. Longitudinal data from the Population Assessment of Smoking and Health surveys (PATH) showed that people making a quit attempt with ENDS were 1.32 (CI 1.03-1.71) times more likely to quit in the past year than those making a quit attempt without ENDS

Please see table 1, answer 6.

(Glasser et al., 2020).

P71L33-4 The US National Health Interview Surveys 2014-2016 for ages 25-44 (N = 26354) shows that 10.1% of current ENDS users reported quitting in the past 12 months compared with 6.3% of those not currently using ENDS, aOR = 1.64 (CI 1.21-2.21). Similar findings were also found in the Tobacco Use Supplement to the Current Population (Johnson et al. 2019).

P70L43-45 A PRISMA-compliant systematic review and meta-analysis by Liu et al. (2018) of 14 studies with 35665 participants calculated an efficiency quit rate from 13.2% - 22.9%. They characterize ENDS as a “promising” cessation aid.

P70L27-8 A review by Franks et al. (2018) in *Pharmacotherapy*, a journal of the American College of Clinical Pharmacy, concludes that ENDS “may have modest effects to help tobacco users achieve cessation” in a number of different patient populations (p. 565). Clinicians are advised to discuss with their patients “all cessation options, including potential benefits and harms of e-cigarette use, is recommended” (p. 566).

P71L1-9 The cessation standard for the Hajek RCT was very stringent, with one year of sustained abstinence, a self-report of smoking no more than 5 cigarettes from 2 weeks after the start date, and biochemical verification of cessation. The analysis applied the intention-to-treat standard with those lost to follow-up and participants not completing the biochemical verification computed as not achieving cessation. This seminal RCT has been cited over 550 times (per Google Scholar). The ENDS participants achieved 17.7% sustained abstinence, compared to the 7.6% quit success rate in the US (US Surgeon General 2020).

A Belgium case report of ENDS use for cessation by patients in treatment with tobacco counselors, at 7 months (n=103, 70 ENDS users) almost 40% had eCo verified abstinence, RR 1.71 (CI 1.04-2.81) compared to NRT users (Adriaens et al., 2019).

Electronic cigarettes are recommended as cessation help by the UK

National Health Services website: Using e-cigarettes to stop smoking. It confirms that “Many thousands of people in the UK have already stopped smoking with the help of an e-cigarette. There's growing evidence that they can be effective.” (<https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/>).

The WHO Study Group on Tobacco Product Regulation (2019) observes that “Whether an ENDS has beneficial or detrimental effects on smoking cessation appears to depend on the technology, the motivation and consumer behaviour of the ENDS user, the type of smoker who seeks ENDS use and the regulatory environment for ENDS and tobacco use” (p. 60).

Ref.

Adriaens, K., Belmans, E., Van Gucht, D., & Baeyens, F. (2019). Effects of implementing the electronic cigarette in the standard quit-smoking treatment by tobacco counselors in Belgium. [Poster presentation]. BAPS [Belgium Association for Psychological Sciences] meeting, 2019/05/14-2019/05/15, Liege, Belgium.

Franks, A. S., Sando, K., & McBane, S. (2018). Do electronic cigarettes have a role in tobacco cessation? *Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy*, 38(5), 555-568.

Liu, X., Lu, W., Liao, S., Deng, Z., Zhang, Z., Liu, Y., & Lu, W. (2018). Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine*, 97(19).

357	Wyszynska-Szulc, Agnieszka, Philip Morris Products S.A., Switzerland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>P. 70 1. 45-51</p> <p>We suggest changing the content of lines 45-51 to capture the latest conclusions from the updated 2020 Cochrane review (Hartmann-Boyce 2020) which concludes based on the analysis of the most recent and relevant clinical trials that there is “moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT.”</p> <p>P. 71 1. 18</p> <p>While this Section discusses if e-cigarettes are effective cessation aids, we suggest that it reflects also the role of flavours in helping smokers switch.</p> <p>We suggest to add the following: “Several studies demonstrate that non-tobacco flavoured and non-menthol flavoured, especially fruit flavoured e-liquids, facilitate the switching of smokers compared to traditional tobacco and menthol flavoured e-cigarettes (Romijnders</p>	<p>Please see table 1, answer 6.</p> <p>In the Opinion, the SCHEER addressed the role of flavours in the use of electronic cigarettes.</p>
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(2019); Havermans (2019), Du (2020), Russel (2018), Gravely (2020), Friedman (2020)).”

P. 71 i. 32
We suggest to add the following: “Recent studies from 2020 demonstrate the effectiveness of nicotine containing e-cigarettes in smoking cessation (Lucchiari 2020; Glasser 2020; Farsalinos 2020, Levy 2020, Hartmann-Boyce 2020).” Several recent studies clearly demonstrating the effectiveness of nicotine containing e-cigarettes in smoking cessation are omitted in the SCHEER’s Opinion. E.g., a randomized control trial by Lucchiari (2020) assessed the effectiveness of e-cigarettes in reducing tobacco consumption and found that participants who used nicotine containing e-cigarettes significantly reduced daily cigarette consumption. After 6 months participants in the nicotine e-cigarette group smoked fewer cigarettes than any other group.

The findings of a paper by Glasser (2020), investigating the patterns of e-cigarettes’ use on smoking cessation using data from 3 waves of the PATH study, and which are consistent with the growing body of evidence from prospective and cross-sectional observational studies, show that more frequent and stable e-cigarettes’ use can help smokers quit smoking, but that intermittent or infrequent use can be associated with poorer smoking cessation outcomes.

Farsalinos (2020) analyzed the association between e-cigarettes’ use and smoking cessation in the EU in 2017 and found that “daily e-cigarette use was positively associated with cessation ≤ 5 years while former daily e-cigarette use was positively associated with smoking cessation of ≤ 2 years.”

Levy (2020) used an indirect simulation model to assess the potential impact of e-cigarettes on smoking prevalence in England. The authors found that “the results indicate that NVPs [nicotine vaping products] played an important role in reducing smoking prevalence in England in 2012-2019. Other studies have found significant impacts of NVPs on smoking cessation and initiation in England.”

In the Opinion, the SCHEER addressed the role of electronic cigarettes effectiveness in helping smokers to quit and reduce smoking. Please see also Table 1, answers 1, 2, 6 and 7.

It is also worth including in the Opinion the practice of the cessation services in some European countries, e.g., the national health agency Santé Publique France and the UK National Health Services acknowledge the role of e-cigarettes in cessation and smoking reduction and recommend (e.g. via their websites: www.tabac-info-service.fr, www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/) switching to e-cigarettes as one of the ways for smoking cessation.

Ref.:

Du 2020 Changes in Flavor Preference in a Cohort of Long-term Electronic Cigarette Users

Farsalinos 2020 Association between e-cigarette use and smoking cessation in the EU in 2017

Friedman 2020 Associations of Flavored eCigarette Uptake With Subsequent Smoking Initiate

Glasser 2020 Patterns of ecigarette use and subsequent smoking cessation over 2 years in PATH study

Gravely 2020 The Association of E-cigarette Flavors With Satisfaction Enjoyment Trying to Quit

Hartmann-Boyce 2020 Cochrane Database of Systematic Reviews

Havermans 2019 Nearly 20 000 e-liquids and 250 unique flavour descriptions - overview of the Dutch market

Levy 2020 The impact of nicotine vaping on smoking prevalence and smoking-attributable deaths in England

Luchinary 2020 Benefits of e-cigarettes in smoking reduction and in pulmonary health

Romijnders 2019 ELiquid Flavor Preferences and Individual Factors Related to Vaping

Russell 2018 Changing patterns of first ecigarette flavor used and current flavors used by adult frequent users

358	Wacław Michalina, Prawo dla Ludzi (Law for People), Poland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	SCHEER states that there is "weak evidence to support the effectiveness of electronic cigarettes in helping smokers quit smoking". We strongly disagree with this view. According to a study by Jackson et al 2019; 'The use of e-cigarettes and varenicline are associated with higher rates of abstinence after trying to quit smoking in England.' There are more such research results. Moreover, only one person taking part in our consultation smokes traditional cigarettes alternately with e-cigarettes. All the rest of the people quit smoking completely.	Thank you for your comment but the SCHEER sufficiently underpinned the conclusion.
359	Sweeney Damian, European Tobacco	6.7 Role of electronic cigarettes in the cessation of	Page 70 lines 21 to 55. Page 71 lines 1 to 34 SCHEER states that data at individual and population level will be taken into consideration in their analysis, at page 10 lines 24-26: "The scientific opinion should address considerations relevant both	Please see table 1, answer 6.

Harm Reduction Advocates, Ireland	traditional tobacco smoking and dual use	<p>at individual level and at a population level, from a public health perspective.” However, the report fails to do this. Randomised Control Trials and population level data from national surveys across Europe show that vaping is effective for smoking cessation.</p> <p>Two randomised control trials are cited in the opinion, Hajek, et al (2019) and Walker et al (2020), both of these studies show e-cigarettes to be significantly more effective than NRT’s. In the case of Hajek et al, e-cigarettes were 83% more effective than NRT’s, and Walker et al found e-cigarettes combined with NRT’s to be 2.5 times more effective than patches alone. The most recent Cochrane review concluded that e-cigarettes were 68% more effective than NRT’s (Hartmann-Boyce et al., 2020). In their study: Moderators of real-world effectiveness of smoking cessation aids: a population study, Jackson et al (2019) conclude that “Use of e-cigarettes and varenicline are associated with higher abstinence rates following a quit attempt in England”. A recent study by Lucchiari et al (2020) concluded that participants who used e-cigarettes with nicotine smoked fewer tobacco cigarettes than any other group after 6 months. Glasser et al (2020) added further evidence to the efficacy of e-cigarettes in their study which found that smoking cessation was more likely among frequent e-cigarette users.</p> <p>Data from national surveys provide strong evidence that e-cigarettes have contributed to a reduction in smoking prevalence. The Health Ireland survey for 2019 shows that smoking prevalence fell 6% in 3 years with 38% of successful quitters using e-cigarettes, compared to only 15% using pharmacological products. Santé Publique France found that more than 700,000 people have used e-cigarettes to stop smoking in the long term in 2017 and that vaping is the most common method used to quit smoking in France (Pasquereau et al., 2017).</p> <p>Population data from the USA found that “The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level” (Zhu S-H et al, 2018)”</p> <p>Ref.: Hajek (2019). A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy</p>
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			<p>Lucchiari (2020). Benefits of e-cigarettes in smoking reduction and in pulmonary health among chronic smokers undergoing a lung cancer screening program at 6 months</p> <p>Zhu (2017). E-cigarette use and associated changes in population smoking cessation evidence from US current population surveys</p> <p>Hartmann-Boyce (2020). Electronic cigarettes for smoking cessation Review Cochrane 2020</p> <p>Jackson (2019). Moderators of real-world effectiveness of smoking cessation aids Healthy Ireland Summary Report 2019; pages 3-4</p> <p>Glasser (2020). Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years</p> <p>Usage de la cigarette électronique. French MoH poll 2017</p>	
360	<p>Vape Business Ireland</p> <p>Vape Business Ireland, Va pe Business Ireland, Irel and</p>	<p>6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use</p>	<p>We disagree that “The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation” (Page 71, Line 21)</p> <p>In spite of the fact that "the authors noted that there is evidence from two trials that electronic cigarettes help smokers to stop smoking in the long term compared with placebo electronic cigarettes" (Page 70, Line 45-51), the Opinion states that confidence in the results of the Cochrane Review are low due in part to wide confidence intervals and low event rates. Importantly however, this review examined early generation vaping products, which do not deliver nicotine as effectively as newer generation devices (Yingst, Hajek) which can affect success in quitting. The most recent review by the Cochrane Collaboration (Jamie Hartmann-Boyce et al. 2020) considered the results of 50 studies in 15 countries and confirm their earlier finding that vaping products help people quit smoking and that they are safe to use and increased their confidence to moderate. A recent analysis of 13,057 current and former smokers in 28 EU countries, which is not cited in the report, found that current vaping product users were almost five times more likely to have quit smoking in the last two years than non-vapers and more than three times more likely to have quit in the last three to five years (Farsilinos and Barbouni 2020). A 2019 study (Beard et al.) showed that, as vaping product use has increased in England, so too has the rate of successful quit attempts, as well as the overall number of quit attempts. Notably the country with the lowest smoking rate in the EU, Sweden (7%) has a regulatory environment which is supportive of reduced-risk alternatives to cigarettes, such as e-cigarettes and snus.</p>	<p>Please see table 1, answer 6.</p>

In several places, SCHEER appears to down-play and mischaracterise smokers use of vaping products. For example, on Page 70, LINE 31, Filippidis 2019 is incorrectly cited as reporting that during the study time frame "experimentation with the use of electronic cigarettes for smoking cessation increased..." This is a mischaracterisation of the data. Filippidis did not question participants regarding experimentation, but instead asked smokers which methods they used to quit smoking. Page 70, line 38 of the Opinion reads, "...use of cessation assistance among a cohort of smokers from eight European countries indicated that experimentation with electronic cigarettes as a smoking cessation device in the last quit attempt differed substantially across different European Member states..." citing Hummel et al 2018. Here too the use of the word "experimentation" misrepresents and mischaracterises the data in Hummel's study. Experimentation may infer a lack of seriousness, frivolity, or even recreational use. None of these concepts were part of the official study. We agree that strategies to help smokers quit are essential to public health as stated on Page 70, Line 27-29, but current strategies are clearly inadequate and do not effectively address the EU's high levels of smoking (26%). SCHEER's conclusion is arrived by pooling findings from different studies, not adjusting for population/race differences, age and sex, and different durations of cessation (seven days to 12 months). A 12-month abstinence differs substantially from seven days. A thorough objective and unbiased scientific evaluation of the weight of evidence for vaping products and their role in cessation and effectiveness in helping smokers move away from smoking therefore should have arrived at 'strong' conclusion instead of 'weak'.

Ref:

Beard E, West R, Michie S, Brown J (2019) Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time series analysis between 2006 and 2017 *Addiction* (Abingdon, England) 0 doi:10.1111/add.14851)

Hartmann-Boyce (2020) *Cochrane Database of Systematic Reviews*

361	Compernelle Thomas,Br	6.7 Role of electronic cigarettes in the	The SCHEER Opinion evaluated the strength of evidence as "weak" for cessation, and "weak to moderate" for reduction, lacking the proper justification for these determinations and ignoring the	Please see table 1, answer 6.
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British
American
Tobacco, Belgium
and dual use

scientific evidence. While e-cigarettes are not authorised cessation devices, millions of smokers around the world have successfully switched to using e-cigarettes (1-6). Several studies, including randomised control trials and observational studies have shown that e-cigarettes are effective in helping adult smokers to quit smoking successfully (5,7-16). Rates of cessation using e-cigarettes have been reported as being as similar to or higher than standard cessation methods (3,17-18), even twice as effective as abstinence or NRT (19-20). A recent study of 13,057 subjects from 28 EU countries, found that compared with former smokers who had never used e-cigarettes; daily e-cigarette users were 5 time more likely to have quit smoking (21). In the EU, 6 out of 10 people reportedly took up e-cigarettes to stop or reduce tobacco consumption and was the highest mentioned reason for using e-cigarettes (61%) (22). More recently, a Cochrane review, across 50 global studies, including EU countries (Italy, Belgium, Greece and Poland) undertook an evidence synthesis that focused on the available RCTs and found an association between e-cigarette use and higher quit rates vs NRT vs non-nicotine e-cigarettes vs support only/no support (23).

SCHEER treated cessation as a monolith, when in fact measures of cessation varied considerably and were often unique outcomes that should not be grouped as a collective, e.g., 7-day point prevalence abstinence is a far different outcome than 12-month abstinence. The outcome measures should have been described and appropriately considered as unique measures (24). Failure to do so compromises the validity of the weight of evidence evaluated.

Comparator groups and e-cigarette use definitions were highly variable in the included studies and included NRT, nicotine-free e-cigarettes, and support/counselling (19, 24-27). Frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation (24) was not considered. Adjustment for confounders, between study groups within a given study were also not considered as well as a number of other important confounding factors. One study found African American participants were more likely to use e-cigarettes as a cessation aid

compared to Caucasians (p = 0.03) (28).

Intention to quit and nicotine dependence varied across studies and study participants. Respondents with a higher motivation to quit are more likely to have a successful quit attempt.

In a recently completed systematic review and meta-analysis on associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking, 101 studies were identified as investigating the association between e-cigarette use and abstinence from cigarette smoking. Among those studies, the majority (76%) did not adjust for age, race, and sex (29).

Thus, pooling a body of evidence with high heterogeneity among studies, lacking adjustments for confounding factors that influence observed associations between e-cigarette use and smoking cessation outcomes, will inherently result in the evidence being graded as “weak.” This issue was discussed in a systematic review included in the Opinion’s assessment of cessation (26). We therefore respectfully request SCHEER to re-evaluate their conclusion, considering the available literature demonstrating their role in cessation and effectiveness in help smokers to quit.



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362 No agreement to disclose personal data	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>As we indicated in previous comments, the role of electronic cigarettes in smoking cessation should not be underestimated. There is a strong evidence available in many EU countries; the Eurostat survey shows a similar trend. These data show that electronic cigarettes are by far the most widespread tool for smoking cessation compared to nicotine replacement therapies. (See: Special Eurobarometer 458, Attitudes of Europeans towards tobacco and electronic cigarettes)</p> <p>Since 2019 in the Czech Republic the role of electronic cigarettes is embedded in National Strategy to Prevent and Reduce the Harm Associated with Addictive Behaviour 2019-2027, approved by Czech government in 2019.</p>	Thank you for your comment but the SCHEER sufficiently underpinned the conclusion.
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(https://www.vlada.cz/assets/ppov/protidrogova-politika/National_strategy_2019_2027_fin_rev3.pdf)

They have clearly attributed role in smoking cessation and harm reduction efforts.

363 Michel Nicolas, Association Romande des Professionnels de la Vape, Switzerland

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Cessation Page 8, lines 34 to 46

What this report fails to say, when it cites precisely these data: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6317445/> Younger people were more likely to have reported e-cigarette use for smoking cessation but less likely to have used a cessation service. We see here that the use of vaping as a smoking cessation tool has increased as vaping has become more common / accessible and that vaping appears to be a more attractive method of quitting, especially for young people, than traditional methods. Vape as a cessation tool, although it should not prove to be more effective than another method, is interesting since it is more attractive than traditional methods. It is also possible that it affects another segment of smokers. This report indicates that the reasons for using vape among young people are curiosity, the price or the possibility of vaping in places where smoking is prohibited. If it turns out that this can lead young people to quit smoking when they would not have considered another method of quitting, it means that its effectiveness - even relative - become in addition to other methods of smoking cessation.

Thank you for your comment but the SCHEER sufficiently underpinned the conclusion.

Page 71

There is a lack of robust longitudinal data on the effect of electronic cigarettes on smoking cessation.

Thank you, noted.

Page 70

45 To this extent, a Cochrane Review Your opinion was published just before a Cochrane data update. You should therefore update your review based on the latest information, especially as you indicate that they are necessary and may change your conclusion: "More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement " https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used

Please see Table 1, answer 6.

If after including the latest information available you persist in considering that the scientific evidence is not strong enough to determine if vaping is an effective quit smoking aid, you can have another point of view. You will no doubt admit that some people have managed to quit smoking thanks to the vape, so we can say: In some cases vaping help to quit smoking but in the majority of cases the attempt to quit fails. With a reported failure rate of 80-97%, the same can be said of all other methods. There's no efficient tool to stop smoking. The question is therefore not whether vaping is more ineffective or less ineffective than other methods, but to consider that no single method will end the game alone and that it is a set of measures which, combined, represent the best hope. In this context, vaping has a role to play: It has allowed some people to quit smoking and in the countries where vaping is the most comon, the smoking prevalence is declining.

364	No agreement to disclose personal data	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	I do not agree with the results of the study regarding the effectiveness of the electronic cigarette in smoking cessation. I was a heavy smoker. I tried most of the available solutions (patch, gums, acupuncture ...) to stop smoking without success. I tried the electronic cigarette and in three weeks I succeeded in quitting smoking. I haven't had a cigarette for 5 years. In my experience the electronic cigarette is the most effective and cheapest solution for society to stop smoking.	Thank you for your comment.
365	Bamberger Claude,Aid uce,France	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Not a single study since vaping appeared showed less efficiency of regular vaping with nicotine than average stopping methods (and most showed more adoption in countries with a neutral or positive position about vaping). Most post-2015 studies (i.e. more or less about current vaping products) showed an increase of short and long term quit rate compared to the most used and recommended methods. At a point for Cochrane to assess in a Review, Hartmann-Boyce et al 2020 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full (reference citation uploaded)</p> <p>"There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared</p>	Please see table 1, answer 6.

to NRT." After having already assessed years ago its short term positive effect on smoking reduction and cessation like many health agencies (including OFDT in France) on local data. The Scheer report already assessed Hajek et al 2019 (how can a two fold superiority in an RCT be "weak evidence for the support of electronic cigarettes effectiveness" ? "The 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group" Hajek when confirmed by Jackson et al 2019 <https://onlinelibrary.wiley.com/doi/10.1111/add.14656> (reference citation uploaded)

"Use of e-cigarettes and varenicline are associated with higher abstinence rates following a quit attempt in England." by Lucchiari et al., 2020 <https://pubmed.ncbi.nlm.nih.gov/31838445/> (reference citation uploaded)

"After 6 months about 20% of the entire sample stopped smoking. Participants who used e-cigarettes with nicotine smoked fewer tobacco cigarettes than any other group after 6 months ($p < 51 .020$). Our data add to the efficacy and safety of e-cigarettes in helping smokers reduce tobacco consumption and improving pulmonary health status." and illustrated by Pasquereau et al., 2017 https://www.researchgate.net/publication/337542002_USAGE_DE_LA_CIGARETTE_ELECTRONIQUE_TABAGISME_ET_OPINIONS_DES_18-75_ANS_Barometre_de_Sante_publicque_France_2017 (uploaded)

"The number of daily ex-smokers who have quit smoking for more than six months and who believe that vaping has helped them quit smoking is estimated at around 700,000 since the arrival of the e-cigarette on the market in France" (the total number of people who vaped regularly and stopped smoking with or without quitting vaping at that time was 1.4 millions in France according Eurobarometer from the closest period) or by Van Gucht, Adriaens and Baeyens, 2017 <https://www.mdpi.com/1660-4601/14/7/798> (uploaded)

"99% of those surveyed smoked before vaping. 81% agreed they could quit smoking with vaping, compared to traditional cessation aids. 84% experienced improvements in health."

The current evidence of smoking reduction in regular vapers is strong (not a single study showed otherwise) as well as for cessation, and there is moderate evidence of superiority to existing methods in studies.

But as EBM principle show greater adoption rate is as much key as efficiency, and the comparison of growth between NRT and vaping omit that the adoption is not even in the same order in countries adopting a neutral or positive attitude on vaping, it would not be reasonable to qualify such facts as "weak evidence" (for the scale, in France in 2017 when Santé Publique France confirmed at least 700 000 citizen quit smoking thanks to vaping, and according a generous success rate of 10% with NRT in two month treatment there were less than 100 000 ex-smokers successful with NRT based on OFDT data).

366 Poulas Konstantinos, Department of Pharmacy, University of Patras, Greece

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

There is some evidence that e-cigarettes are successful in aiding smokers to quit smoking and it was not included in the SCHEER's Preliminary Opinion and thus the role of electronic cigarettes in the cessation of smoking, are undermined. According to our recent publication (Farsalinos et al, 2019):

Current and current daily e-cigarette use are strongly associated with recent smoking cessation in Greece, suggesting a positive public health impact in a country with the highest prevalence of smoking in the European Union. E-cigarettes do not appear to promote relapse in long term former smokers. Duration of smoking cessation and frequency of e-cigarette use should be taken into consideration when examining the association between e-cigarette use and smoking cessation in population studies.

For more info: Intern Emerg Med 2019 Sep;14(6):835-842. doi: 10.1007/s11739-018-02023-x.

Thank you for your comment but the SCHEER sufficiently underpinned the conclusion.

367 Sebrie Ernesto, Campaign for Tobacco-Free Kids, United States

6.7 Role of electronic cigarettes in the cessation of traditional

In October 2020, The Cochrane Library's Tobacco Addiction Group published a review of the evidence regarding the role of e-cigarettes in quitting smoking.

Citation: Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Ntley C, Rigotti NA, Turner T, Butler

Thank you for your comment. Please see Table 1, answer 6.

d States of tobacco smoking
America and dual use AR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216

This review concludes that “There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT.” While it deserves consideration, this review should not change the committee’s conclusion that “Regarding the role of electronic cigarettes in cessation of traditional tobacco smoking, the SCHEER concludes that there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit...”

The 2020 Cochrane review, while a comprehensive assessment of the evidence, relies on just four studies to reach its main conclusions regarding the effectiveness of e-cigarettes for cessation. The review itself acknowledges that the evidence remains limited, noting that their results are based on a small number of studies and that “we need more, reliable evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery.” Of the four studies submitted (Bullen 2013, Hajek 2019, Lee 2018, Lee 2019,) two are already within the scope of the Committee’s Preliminary opinion:
- Hajek 2019 (discussed on page 71, lines 1-9).
- Bullen 2013 was one of two RCTs eligible for meta-analysis in Cochrane’s 2016 review of electronic cigarettes for smoking cessation (discussed on page 70, lines 45 to 51).

The other two studies were conducted in specific populations: Lee 2018 evaluated smoking cessation in a group of veterans and Lee 2019 only tested males.

More broadly, the four studies are subject to important limitations:
- Firstly, the results are not generalizable to all smokers. Two studies included only smokers who were motivated to quit and sought help in doing so (Bullen 2013 and Hajek 2019) while another study included only males (Lee 2019) and another was limited to preoperative veterans (Lee 2018.)

- Secondly, the types of e-cigarette devices examined in the studies vary and none of the studies included newer pod products, that deliver high doses of nicotine. These products now dominate the U.S. market and are being introduced in many EU countries. E-cigarettes vary widely, including in how much nicotine they deliver, how efficiently, and for how long. More studies are needed before there is enough evidence to make a categorical statement about the efficacy of e-cigarettes as quit aids, particularly when compared to other safety-tested, evidence-based cessation aids.

- Lastly, the studies don't speak to the efficacy of e-cigarettes on their own. Three of the studies examined the effectiveness of e-cigarettes combined with another intervention, such as counseling or other behavioral support, making it impossible to determine if e-cigarettes would be effective for cessation if not used in combination with additional support.

- It should also be noted that the conclusions of the review are only based on quitting at six months and do not take into account what proportion of smokers may relapse into smoking or dual use of e-cigarettes and cigarettes after the initial six months. One recent study found that six months is not a good predictor of long-term quitting success (Chen 2020.) Chen, R, et al. E-cigarette Use to Aid Long-term Smoking Cessation in the US: Prospective Evidence from the PATH Cohort Study. *American Journal of Epidemiology* (2020).

Ref:

Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD010216

Chen et al (2020). Use of Electronic Cigarettes to Aid Long-Term Smoking Cessation in the United States: Prospective Evidence From the PATH Cohort Study. *Am J Epidemiol* . 2020 Dec 1;189(12):1529-1537. doi: 10.1093/aje/kwaa161. DOI: 10.1093/aje/kwaa161

368	Sebrie Ernesto, Campaign for Ca mpaign for	6.7 Role of electronic cigarettes in the	Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16 A study published in September 2020 analyzed data on daily	Thank you for your comment.
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Tobacco-Free Kids, United States of America

cessation of traditional tobacco smoking and dual use

smoker adults in the US from several successive waves of the PATH study. The authors found no significant difference in abstinence from cigarettes 1-2 years after a quit attempt made with or without using an e-cigarette. These data are particularly important because much of the available smoking cessation research only follows users for 6 months post-quit attempt. Citation: Pierce J P, Benmarhnia T, Chen R, White M, Abrams D B, Ambrose B K, et al. (2020) Role of e-cigarettes and pharmacotherapy during attempts to quit cigarette smoking: The PATH Study 2013-16. PLoS ONE 15(9):e0237938. Available at: <https://doi.org/10.1371/journal.pone.0237938>

Smoking Cessation and Vaping Cessation Attempts among Cigarette Smokers and E-Cigarette Users in Central and Eastern Europe

A study published in January 2020 analyzed survey data from university students across Central and Eastern Europe (n=1716 exclusive smokers, n=129 exclusive e-cigarette users, and n=216 dual users.) The study found no significant difference in quit attempts or willingness to quit between dual users and exclusive smokers. This study, while relatively small, merits consideration in section 6.7 because it suggests that young adults in Europe are not using electronic cigarettes as cessation devices, regardless of e-cigarettes effectiveness or lack thereof as a cessation aid.

Ref:

Jankowski M et al. Smoking Cessation and Vaping Cessation Attempts among Cigarette Smokers and E-Cigarette Users in Central and Eastern Europe. Int J Environ Res Public Health. 2020 Jan; 17(1): 28.

369 Posch Waltraud, Austrian Association of Addiction Prevention, Austria

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Electronic cigarettes are advertised as cessation in many cases. This argument includes that smokers are not willing or not able to stop nicotine consumption. But that's mostly not the reality: Many people managed to stop smoking all over the world without electronic cigarettes. In Austria nearly a quarter (!) of the population quit smoking.

From the point of view of addiction prevention it is not "cessation" if someone switches from one nicotine product to another. Another

Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

nicotine product can at most be the next step on the way to real cessation. That's possible theoretically. In reality most people who switched from tobacco cigarette to electronic cigarette don't see any reason to stop nicotine consume. Because they are told that the switch is already their goal, the cessation.

The risk staying addictive to nicotine is much bigger by using electronic cigarettes compared with pharmacological nicotine replacement therapy and compared with using nothing.

Seen in a longterm view, the most common kind of consuming electronic cigarettes seems to be the dual use (tobacco cigarette and electronic cigarette).



6.7_Role_in_cessation_of_tobacco_and_dual

370 Farsalinos Konstantinos, University of Patras, Greece
6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Page 70, line 18 to page 71, line 34. It is particularly concerning that the authors of the Scheer report concluded that there is weak evidence for the support of e-cigarettes' effectiveness in helping smokers to quit. The report cited two randomized controlled trials which clearly showed that e-cigarettes were more effective than NRTs [1,2]. It should be reminded that the latter are approved for smoking cessation. Furthermore, an updated Cochrane review report recently analyzed 50 studies and concluded that is moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and compared to NRTs [3].

A recent analysis of the 2017 Eurobarometer survey reported that, compared to never e-cigarette use, daily e-cigarette use was associated with 5-fold higher odds of being a former smoker of ≤ 2 years (adjusted prevalence ratio: 4.96, 95% CI 3.57 to 6.90) and 3-fold higher odds of being a former smoker of 3-5 years (adjusted prevalence ratio: 3.20, 95% CI 2.10 to 4.87) [4]. Even former e-cigarette use was associated with higher odds of being a former smoker of ≤ 2 years compared to never e-cigarette use (adjusted prevalence ratio: 1.96, 95% CI 1.21 to 3.12) [4].

Please see table 1, answer 11.

Furthermore, the authors present the conclusions mentioned in the European Heart Network report (EHN 2019) and in the 2020 US Surgeon General Report, which seem to have played a major role in their decision to report that there is weak evidence for the support of e-cigarettes' effectiveness in helping smokers to quit. It should be emphasized that it is not the role of the Scheer report to present or use opinions of other documents in making any conclusions, since the other reports do not appear to represent systematic reviews of evidence. This is highly inappropriate and does not serve the purpose and goals of the Scheer report.

The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.

I strongly support the conclusion of the latest Cochrane review that there is moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and compared to NRTs [3].

Please see Table 1, answer 6.

1. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. *N Engl J Med.* 2019 Feb 14;380(7):629-637. doi: 10.1056/NEJMoa1808779.
2. Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med.* 2020 Jan;8(1):54-64. doi: 10.1016/S2213-2600(19)30269-3.
3. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev.* 2020 Oct 14;10:CD010216. doi: 10.1002/14651858.CD010216.pub4.
4. Farsalinos KE, Barbouni A. Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries. *Tob Control.* 2020 Feb 3;tobaccocontrol-2019-055190. doi: 10.1136/tobaccocontrol-2019-055190.

371	Schmidt Norbert, Int ernessenge meinschaft E-Dampfen e.V. (IG-ED), Germany	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	P 70 L 45-51	The Cochrane report was recently updated and states: "We are moderately confident that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy or nicotine-free e-cigarettes." Ref: Hartman-Boyce (2020) Electronic cigarettes for smoking cessation (Review)
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Please see Table 1, answer 6.

372	Naughton Felix, University of East Anglia, United Kingdom	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>I wanted to raise the topic of e-cigarette use during pregnancy as a means to promote abstinence from tobacco, as this was not covered in the chapter concerning e-cigarettes as a means to promote abstinence from smoking. The below also has relevance for other chapters of the report.</p> <p>A substantial proportion of female smokers quit smoking upon discovering they are pregnant. This is estimated at between one third and one-half of smokers who become pregnant, though with variation based on study and country. However, if women do not quit in the first few days after discovering they are pregnant, they are very unlikely to quit https://pubmed.ncbi.nlm.nih.gov/25016042/. In a cohort study we have undertaken in the UK, we found only 15% of pregnant women who were smokers at their first maternity scan (~14 weeks gestation) self-reported as abstinent by the end of pregnancy https://pubmed.ncbi.nlm.nih.gov/29146659/. In one of our UK trials looking at digital support to help abstinence in pregnancy, we used a robust outcome of biochemically verified continued abstinence from mid-pregnancy to the end of pregnancy, and found only 2% of our control arm (receiving ‘usual care’) had achieved verified continued abstinence https://pubmed.ncbi.nlm.nih.gov/28239919/. We know that tobacco has very serious effects on pregnancy and foetal outcomes. But the evidence is clear – among those female smokers who don’t quit immediately upon discovering they are pregnant (up to one-half) very few succeed in quitting thereafter during their pregnancy. This is not due to a lack of motivation. In the trial cited where only 2% of control participants were confirmed as abstinent, 99% of the sample agreed to some extent with the statement ‘smoking during pregnancy can cause serious harm to my baby.’</p> <p>E-cigarettes may represent a harm-reduction approach for such women who are unable to quit during pregnancy, which is a large proportion of those who do not quit soon after discovering they are pregnant as highlighted above. A minority of pregnant women already use e-cigarettes, 5% in our recent UK survey study https://pubmed.ncbi.nlm.nih.gov/33012050/ and as highlighted earlier in the SCHEER report. A recent review</p>	<p>The SCHEER agrees with the comment on pregnancy but the comparison with traditional smoking is out of the scope of this Opinion.</p>
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<https://pubmed.ncbi.nlm.nih.gov/32621526/> has found no evidence of harm from nicotine replacement therapy (NRT) in humans during pregnancy, suggesting if there is harm, it is likely to be small. While e-cigarettes are not considered harmless, there is consensus that they represent a reduced harm product compared to smoking. And the evidence so far indicates that e-cigarettes are likely to confer only a fraction of the harm from tobacco. This is very likely to be the case for pregnancy too. A UK collaboration (including myself) is currently investigating the efficacy of e-cigarettes for smoking cessation during pregnancy (funded by the English National Institute for Health Research). I feel consideration of the potential for e-cigarettes to reduce harm from tobacco during pregnancy is worthy of comment in the report.

373	Lund Karl Erik,Norwegian Institute of Public Health,Norway	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>P 70 L 43 ff: - when discussing the effect from e-cigarettes in smoking cessation, the report refer to conclusions in European Heart Network (EHN 2019) (not listed in references) and a US Surgeon General Report (SGR 2020). Please note that the report from EHN is a policy paper and not a systematic review, and that the SGR does not conduct an original and independent self-review of the evidence. Please also note that an updated Cochrane-report recently has been published comprising 50 studies (35 are new), representing 12,430 participants, of which 26 are RCTs (Hartman-Boyce et al. 2020). The conclusion was "There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT."</p>	Please see table 1, answer 11.
374	Sproga Maris,Smoke Free Association of Latvia,Latvia	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Page 70 SCHEER's opinion does not consider the fact that e- cigarettes are successful in helping smokers to quit. It ignores unfortunately many recent publications and strong evidence of the effectiveness on electronic cigarettes in smoking cessation. The opinion could also include study by Lucchiari (2020), which demonstrate the effectiveness of nicotine containing e-cigarettes in smoking cessation. E-cigarettes are also recommended as the means of cessation by the UK National Health Services website: Using e-cigarettes to stop smoking, and confirms that "Many thousands of people in the UK have already stopped smoking with the help of an e-cigarette. There's growing evidence that they can be effective."</p>	Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

[\(https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/\)](https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/).

Ref:

Luchiaro 2020 Benefits of e-cigarettes in smoking reduction and in pulmonary health. doi: 10.1016/j.addbeh.2019.106222.

375 Olteanu Vlad, Juul Labs Inc., Belgium
6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Page 70, Line 27-29: 'Due to the large health benefits of smoking cessation for both the individual and public health overall, it is essential to implement strategies to assist smokers in quitting.' Research shows that the vast majority of smokers in the EU are not quitting (Papadakis et al. 2020). The results of the 2020 EUREST-PLUS ITC Europe Surveys* (Papadakis et al. 2020) showed that in all countries studied, the majority of smokers reported that they did not make an attempt to quit smoking in the previous 12 months, have never tried to quit smoking and do not intend to quit smoking in the next 6 months. An exception is England, which has one of the highest reported quitting rates in the EU and where e-cigarettes are the most popular self-reported quitting aid. This is supported by the results of the 2020 UCL Smoking Toolkit Study, which shows that the proportion of people who have successfully quit smoking this year in England is at its highest in more than a decade. There has been an increase of almost two thirds in the quitting success rate, and smoking prevalence in England is at an all-time low of 13.9%. Papadakis et al 2020 conclude that approaches to quitting smoking need to be re-examined in the EU including increasing the use of quit support. They note that in the UK where e-cigarette use is supported by the government and public health bodies, more than half of quit attempts are made with the help of e-cigarettes, demonstrating the relationship between e-cigarette use, successful quitting and a receptive regulatory environment. Given that smokers in the EU are not quitting, any plateau/declines are likely a consequence of young people not starting rather than smokers quitting. This means that there is an aging population of hard-to-reach smokers who are now at increasing risk of severe and potentially fatal illness onset in their later years. Millions of smokers across the EU are now, therefore, most at risk of developing an avoidable cancer and therefore a sub-population that would benefit greatly from the Commission's Beating Cancer Plan prevention efforts. Page 71, Line 1- 17: Randomised controlled trials

Strategies to quit smoking are outside of the scope of this Opinion.

(RCTs) are the gold standard for studying causal relationships between interventions and outcomes. Randomisation eliminates most of the bias inherent with other study designs. Both RCTs cited in the report (Hajek et al. 2019) and (Walker et al. 2019) conclude that e-cigarettes are effective smoking reduction and cessation tools and are at least twice as effective as NRTs. A more recent RCT (Hatsukami et al. 2020) also concluded that smokers incentivised to use e-cigarettes are more likely to quit smoking and do so at significantly higher rates than those encouraged to use NRTs. Page 71, Line 21-28: “The evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation”. The conclusion of the 2020 US Surgeons General report that e-cigarettes, in general, do not increase smoking cessation, is at odds with the results of a US National Institutes of Health-funded study (Zhu et al 2017), which concluded that the first statistically significant increase in population smoking cessation in the US in nearly a quarter of a century was associated with a substantial increase in e-cigarette use among US adults. Page 71 Line 33-34: ‘There is a lack of robust longitudinal data on the effect of electronic cigarettes on smoking cessation.’ In the hierarchy of evidence, RCTs represent the gold standard of scientific research. Several RCTs (Hajek et al. 2019, Walker et al. 2019, Hatsukami et al. 2020) show that e-cigarettes clearly displace smoking, a finding that is supported by Population Studies (Zhu et al. 2017) Observational studies (Jackson et al. 2019) and Scientific Reviews (PHE2020).

Ref:

Hartmann-Boyce et al (2020). Electronic cigarettes for smoking cessation (Review). Cochrane Database of Systematic Reviews. DOI: 10.1002/14651858.CD010216.pub4
Hatsukami et al (2019). A Randomized Clinical Trial Examining the Effects of Instructions for Electronic Cigarette Use on Smoking-Related Behaviors and Biomarkers of Exposure. doi:10.1093/ntr/ntz233
Papadakis et al (2020). Quitting behaviours and cessation methods used in eight European Countries in 2018: findings from the EUREST-PLUS ITC Europe Survey. doi:10.1093/eurpub/ckaa082
McNeill (2020) Vaping in England: an evidence update including mental health and pregnancy, March 2020
Zhu et al (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. British Medical J 2017; 358 : j3262 <https://www.bmj.com/content/358/bmj.j3262>

376 Schweinshaller Peter, CEDT, EU organisation
 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use
 6.7 page 70. The European Confederation of Tobacco Retailers (CEDT) represents 160.000 family businesses and tobacco retailers that create a consolidated network of shops in Italy, France, Spain, Austria, Greece, Hungary, Belgium and Germany. This network may count on more than 45 million European citizens who are visiting these shops every day.
 Thank you for your comment.

Based on our daily experience, we would like to bring to the attention the fact that – more commonly – European consumers approach to electronic cigarettes is essentially different from the one of consumers from the USA and Canada. In fact, our daily contact with European consumers shows that e-cigarettes are mostly bought by the middle generation that is looking for a way to reduce or stop smoking.

As tobacco retailers we think that the e-cigarettes’ impact on tobacco cessation should be considered as moderate.

3.2 page 16. we would like to underline that the use of old data could bring to wrong interpretation of a market that is always evolving and changing. Also, there are many references to the USA or New Zealand market situation and this could be misleading as well.

377 Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and
 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use
 Page 70, lines 43-55
 SCHEER references the 2016 Cochrane Review on e-cigarettes (Hartmann-Boyce, 2015), which included 24 studies, 3 of which were RCTs. SCHEER cited the small number of trials as one of the reasons why it rated the result as “low” by GRADE standards. However, an updated 2020 Cochrane Review is now available and includes 50 studies, 26 of which are RCTs, providing a far more robust review of the role of electronic cigarettes in smoking cessation.
 Please see table 1, answer 11.
 In addition to reinforcing the relative safety of e-cigarettes, the 2020 Cochrane Review found with moderate-certainty evidence that (i) e-cigarettes with nicotine are 70% more effective in helping smokers to successfully quit than nicotine replacement therapy (NRT) and (ii) 70% more effective in helping smokers to successfully quit than nicotine-free e-cigarettes.

	15 from the EU		SCHEER should take this new information into account. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4	
378	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Page 70, lines 36-41 A recurring concern is the fact that this SCHEER often fails to discuss e-cigarette use in a context that includes comparisons to smoking. For example, in discussing quit attempts, England is listed as having the highest percentage of people using electronic cigarettes in their last cessation attempt (51.6%), but no mention is made of the fact that England also has the lowest smoking rate among European countries (14.1% smoking rate for persons 18 years and older). Page 71, lines 21-28 While SCHEER cites the US Surgeon General's 2020 Report on Smoking Cessation, SCHEER fails to cite the position of Public Health England, which has long championed e-cigarettes as a smoking cessation tool in a country which has, not coincidentally, achieved the lowest smoking rate in Europe. (McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products 2018: a report commissioned by Public Health England. London: Public Health England 2018) Ref: UK Office for National statistics. Adult smoking habits in the UK: 2019. Cigarette smoking habits among adults in the UK, including the proportion of people who smoke, demographic breakdowns, changes over time and use of e-cigarettes. Statistical bulletin	Please see Table 1, answer 1.
379	Woessner Julie, International Network of Nicotine Consumer Organisations	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Page 71, line 19 SCHEER relies heavily (if not almost exclusively) on RCTs, which are generally considered to be the "gold standard" for research on pharmaceutical efficacy. However, research suited to pharmaceutical products is poorly suited to an exploration of the efficacy of electronic cigarettes in connection with smoking cessation, and we encourage SCHEER to give weight to other types	Thank you for your opinion.

	ons (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU		of research exploring this issue.						
			For example, a 2017 study involving an online vape shop in the Netherlands found that 81% of the participants agreed that unlike with other smoking-cessation aids, they could quit smoking due to vaping. (Gucht 2017) Similarly, a convenience sample of vape shop customers found that approximately 62% of the participants were biochemically-verified smoking abstinent, with a majority (91%) reporting they enjoyed vaping more than smoking. (Wagener 2016). These studies explore real world data, which is both useful and informative and should not be ignored.						Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.
			Page 71, lines 30-31						
			SCHEER notes, “In addition, the European Heart Network reported that there is not sufficient evidence until now that electronic cigarettes’ use is an effective mean for smoking cessation.” Use of the phrase “until now” is confusing. More importantly, however, SCHEER fails to note that the European Heart Network paper relies heavily on the US NASEM report. This gives the impression that this is European data, but it is not.						The SCHEER has rephrased the conclusions of the Opinion regarding the health effects accordingly.
			ref: Wagener et al (2016). Examining the Smoking and Vaping Behaviors and Preferences of Vape Shop Customers. http://www.dx.doi.org/10.18332/tpc/65150 Van Gucht et al (2017). Online Vape Shop Customers Who Use E-Cigarettes Report Abstinence from Smoking and Improved Quality of Life, But a Substantial Minority Still Have Vaping-Related Health Concerns. doi:10.3390/ijerph14070798						
380	Solimini Renata,Istituto Superiore di Sanità,Italy	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	I think you can add the recent Cochrane review. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4.						Please see table 1, answer 11.
381	Lowenstein William, SOS addictions, France	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	p.70, lines 18-56 p.71, lines 1-34 It seems that the Scheer opinion does not include data which show the usefulness of electronic cigarettes in the process of quitting smoking nor does it consider recommendations made by English authorities. According to Public Health France (Santé Publique France),						Thank you for your comment. The SCHEER sufficiently underpinned the conclusion. Please see Table 1, answer 11.

supported by data of the 2017 Barometer, an important part of former smokers declare that electronic cigarettes has helped them to quit smoking. In France 700 000 people managed to quit smoking with the help of electronic cigarettes.

The French High Council for Public Health had considered in an opinion concerning "the risks and benefits in the use of electronic cigarettes by the general population" published in 2016, that " the electronic cigarette could be considered as a smoking aid for smokers who wanted to quit" and could be considered as a tool to reduce risks linked to smoking.

The English NHS clearly mentions on their website that " many thousands of people in the UK have already stopped smoking with the help of an e-cigarette. There's growing evidence that they can be effective".
<https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/>

The most recent review published by the Cochrane organization states "Nicotine e-cigarettes probably do help people to stop smoking for at least six months They probably work better than nicotine replacement therapy and nicotine-free-cigarettes. They may work better than no support, or behavioural support alone, and they may not be associated with serious unwanted effects".

See Table 1, answer 6.

Vaping must be considered as a transition. It is a step which enables the user to reduce risks. With regard to data provided, the e-cigarette clearly appears to be currently the most efficient smoking cessation aid, which should be promoted by health professionals.

References

BAROMÈTRE DE SANTÉ PUBLIQUE FRANCE 2017 : USAGE DE LA CIGARETTE ELECTRONIQUE, TABAGISME ET OPINIONS DES 18-75 ans.
<https://www.santepubliquefrance.fr/determinants-de-sante/tabac/documents/enquetes-etudes/barometre-de-sante-publique-france-2017.-usage-de-la-cigarette-electronique-tabagisme-et-opinions-des-18-75-ans>
High Council for Public Health OPINION concerning the risks and benefits in the use of electronic cigarettes by the general population 22 February 2016
<https://www.hcsp.fr/explore.cgi/avisrapportsdomaine?clefr=591>
NHS website <https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to->

382 Moiroud Jean, Fédération Interprofessionnelle de la Vape (FIVAPE), France

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

stop-smoking/
Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>

According to SCHEER, “There is a lack of robust longitudinal data on the effect of electronic cigarettes on smoking cessation.” (p. 71, lines 33-34). However, here are several articles worth mentioning which prove that vaping products are indeed effective in helping people quit smoking:

- On randomized trial: Hajek et al., 2019, have showed that vaping is twice as effective as substitute. Link here: <https://www.nejm.org/doi/full/10.1056/NEJMoa1808779>
- On observational studies: Jackson et al., 2019, <https://onlinelibrary.wiley.com/doi/10.1111/add.14656>
- On population data: Zhu S-H et al, 2018, have found that cigarette sales have decreased thanks to vaping. Link here: <http://www.bmj.com/content/358/bmj.j3262>
- On user experience: many testimonials from users exist and should be taken under consideration. It would not be right to ignore them. Here are a few: <http://www.casaa.org/testimonials/>
- On success rate to quit smoking using vaping products: Brown J, et al. 2014 at the link hereafter: <https://onlinelibrary.wiley.com/doi/full/10.1111/add.12623>
- On the link between vaping and abstinence following a quit attempt: Jackson SE et al. 2019 <https://onlinelibrary.wiley.com/doi/10.1111/add.14656>

Furthermore, there are several ways by which vaping can replace smoking, not only as a quit aid. Here are a few:

- Aid for someone who already wants to quit smoking;
- To offer quitters a pleasurable solution with similar aspects to their habits and encourage them to quit;
- As a solution to cigarette taxation (economic pressure);
- Change of behaviour instead of a conscient effort to quit;
- Prevention from smoking relapse for vulnerable people;
- It can work as a substitute to smoking experimentation for young people and therefore prevent a deeply rooted smoking habit among

Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

young people.

SCHEER should understand that vaping products are not only a stop-smoking aid but also a rival product and rival ‘value proposition’ to smoking. They are reduced-risks products, also known as harm reduction solutions.

As regards harm reduction, please see Table 1, answer 1.

In view of the above, we ask SCHEER to considerably soften its preliminary opinion by taking all these studies and arguments into consideration.

Ref:

Hajek et al. (2019). A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. <https://www.nejm.org/doi/full/10.1056/NEJMoa1808779>

Jackson et al. (2019). Moderators of real-world effectiveness of smoking cessation aids: a population study. <https://onlinelibrary.wiley.com/doi/10.1111/add.14656>

Zhu et al. (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. <https://www.bmj.com/content/358/bmj.j3262>

Testimonials: <http://www.casaa.org/testimonials/>

Brown et al. (2014). Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. <https://onlinelibrary.wiley.com/doi/full/10.1111/add.12623>

383 Pooler Marc,UK Vaping Industry Association,United Kingdom 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Misperceptions about vaping are on the rise – in 2020 Public Health England (22) identified that perception of harm from vaping among smokers was increasingly out of line with the evidence; and that these misperceptions are particularly common among smokers who do not vape.

Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

Queen Mary’s University found in 2019 that e-cigarettes are almost twice as effective as nicotine replacement treatments at helping smokers to quit. (23)

Page 71, line 21 – We disagree that ‘the evidence is inadequate to infer that e-cigarettes, in general, increase smoking cessation’. In spite of the fact that the authors noted that ‘there is evidence from two trials that electronic cigarettes help smokers to stop smoking in the long term compared with placebo electronic cigarettes’, page 70, line 45-51, the opinion states that confidence in the results of the Cochrane Review are low due in part to wide confidence intervals and low event rates. Importantly however, this review examined early generation e-cigarettes, which do not deliver

nicotine as effectively as newer generation devices which can affect success in quitting.

- 58.9% of current vapers are ex-smokers and the proportion has grown year-on-year. (24)
- The most recent review by the Cochrane Collaboration considered the results of 50 studies in 15 countries, and confirmed their earlier finding that e-cigarettes help people quit smoking and that they are safe to use. (25)
- A 2017 study covering the 28 member states of the European Union concluded that e-cigarette use in the EU was positively associated with having quit smoking. Former use of e-cigarettes was also associated with having quit smoking. (26)
- A 2019 study showed that as e-cigarette use had increased in England, so too had the rate of successful quit attempts, as well as the overall number of quit attempts. (27)
- Smoking prevalence among adults in England is at a record low of 13.9% (28) and there has been an increase of nearly a quarter (22%) in quit attempts compared to 2019 and an increase of almost two-thirds in the quitting success rate from 14% to 23%, the highest since at least 2007 (29).
- E-cigarettes helped an additional 50-70,000 smokers in England to quit in a single year. (30)

(22) Public Health England, 2020
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf

(23) Queen Mary's University, 2019

(24) Action on Smoking and Health, 2020

(25) Hartmann-Boyce et al, 2020
 (file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Hartmann-Boyce%20et%20al%202020.pdf)

(26) Farsalinos et al, 2017

(27) Beard et al, 2019

(28) ONS, 2020

(29) UCL Smoking Toolkit Study, 2020

(30) University College London, 2019

384 Pooler Marc,UK Vaping Industry Associatio
 6.7 Role of electronic cigarettes in the cessation of traditional

Notably the countries with the lowest smoking rates in Europe – Sweden (7%) and the UK (13.9%) have regulatory environments supportive of reduced-risk alternatives to cigarettes, for example, both permit e-cigarettes, and Sweden permits snus.

Thank you for your comment.

n,United Kingdom tobacco smoking and dual use

In a number of places, the report appears to down-play and mischaracterise smokers use of e-cigarettes.

- Page 70, line 31 – The report incorrectly cites Filippidis 2019 as reporting that during the study time frame ‘experimentation with the use of electronic cigarettes for smoking cessation increased...’ Filippidis did not question participants regarding experimentation, Filippidis asked smokers which methods they used to quit smoking.
- Page 70, line 38 – The report reads, ‘...use of cessation assistance among a cohort of smokers from eight European countries indicated that experimentation with electronic cigarettes as a smoking cessation device in the last quit attempt differed substantially across different European Member states...” citing Hummel et al 2018.
- Here too the use of the word "experimentation" misrepresents and mischaracterises the data in Hummel's study. Experimentation may infer a lack of seriousness, frivolity or even recreational use but none of these concepts were part of the official study.

Page 70, Line 27-29 – We agree that strategies to help smokers quit are essential to public health, but current strategies are clearly inadequate and maintain the EU’s currently high level of smoking (28%). (31) WHO, 2020

Ref:
<https://www.euro.who.int/en/health-topics/disease-prevention/tobacco/data-and-statistics>

385	Clark Alex, The Consumer Advocates for Smoke-free Alternatives Association (CASAA), United States	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	Pg. Lines 19 - 28 According to a review conducted by the Progressive Policy Institute (PPI) the availability of nicotine vapor products is likely responsible for 60%-80% of the accelerated decline in smoking between 2013-2017. Shapiro, Robert J. “The Impact of Electronic Cigarettes on Cigarette Smoking By Americans and Its Health and Economic Implications (Executive Summary).” Progressive Policy Institute, 1 Aug. 2019, Ref: www.progressivepolicy.org/issues/health-care/the-impact-of-electronic-cigarettes-on-cigarette-smoking-by-americans-and-its-health-and-economic-implications/ .
386	Robson Debbie	6.7 Role of electronic	Page 70, lines 43-55; page 71, lines 1-34

Thank you for your information.

,King's
College
London
,United
Kingdom

cigarettes in the
cessation of
traditional
tobacco smoking
and dual use

The preliminary Opinion states “it is important to assess through reviews of existing evidence, cohort studies and randomised control trials to assess the weight of evidence available”, however the authors do not appear to have been comprehensive in their assessment. Not only does this take up the least amount of space in the preliminary Opinion, it also relied on two systematic reviews that searched up until January 2016 (Hartman Boyce 2016) and February 2016 (Malas et al. 2016) and two recent RCTs (Hajek et al. 2019 and Walker et al, 2020). Whilst these are important studies to include, the authors fail to make use of other evidence such as another systematic review by the Joanna Briggs Institute published in March 2019. This reported nicotine containing e-cigarettes were more effective than nicotine replacement therapy (NRT) for achieving smoking cessation (risk ratio (RR) 1.69 (95%CI 1.26-2.28). This review also includes other RCTs published since the Hartman Boyce et al (2016) review that are not included in the preliminary Opinion (e.g. Baldassarri et al 2018).

Please see table 1, answer 11.

Hartman Boyce et al (2020) have just recently published an update of their Cochrane systematic review, which included 50 studies (adding 35 new studies). They reported that “there was moderate-certainty evidence, limited by imprecision, that quit rates were higher in people randomized to nicotine e-cigarettes than in those randomized to nicotine replacement therapy (NRT) (RR 1.69, 95% CI; 1.25 to 2.27; I2 = 0%; 3 studies, 1498 participants). There was also moderate-certainty evidence, again limited by imprecision, that quit rates were higher in people randomized to nicotine e-cigarettes than to non-nicotine e-cigarettes (RR 1.71, 95% CI 1.00 to 2.92; I2 = 0%; 3 studies, 802 participants).

Observational studies, such as those by Drs Emma Beard and Sarah Jackson of University College London are also missing and of relevance to this part of the report. Their work using robust methods, have estimated that e-cigarettes have contributed to tens of thousands of additional quitters in England. They also demonstrate that NRT bought over the counter does not improve quit success, NRT on prescription only works for certain subgroups of people and although varenicline (Champix) is effective in helping people quit smoking, the use of e-cigarettes is also

effective, but as they are considerably more popular than other cessation aids and have a greater reach, they help more people quit smoking.

Finally, there is a complete lack of inclusion of evidence of how e-cigarettes may help reduce the high smoking rates among people with mental health problems and other high-risk groups. We would like to draw the authors' attention to McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England, which includes a systematic review of the effect of e-cigarette use on smoking cessation in people with mental health problems and evidence that their use may help to reduce smoking.

Refs

Beard et al (2018) *BMJ Open* 8:e016046. doi:10.1136/bmjopen-2017-016046
 Beard et al (2020) *Addiction*, 115: 961– 974. <https://doi.org/10.1111/add.14851>.
 Jackson et al (2019) *Addiction*, 114: 1627– 1638. <https://doi.org/10.1111/add.14656>.
 Hartmann-Boyce et al; *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4.
 The Joanna Briggs Institute (2019) *E-cigarettes for Smoking Cessation Guideline Update: Technical report of evidence review and Summary of Findings*. www.joannabriggs.org

387	Barbouni Anastasia, University of West Attica, Greece	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Page 70 / Lines 21-55.</p> <p>A holistic approach based on all scientific evidence will lead to better Public Health decisions.</p> <p>The SCHEER Preliminary Opinion focuses mostly on the youth attractiveness and on health impacts compared to non-smoking and less at the potential harm reduction effects that the e-cigarettes could have in adult smokers that have tried several times unsuccessfully to quit smoking.</p> <p>Furthermore, the evidence that e- cigarettes are successful in helping smokers to quit smoking was not reflected in the SCHEER opinion. Examples from our research have shown that: a. “Current and current daily e-cigarette use are strongly associated with recent smoking cessation in Greece, suggesting a positive public health impact in a country with the highest prevalence of</p>
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Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

			<p>smoking in the European Union” (Farsalinos 2019, E-cigarette use is strongly associated with recent smoking cessation: an analysis of a representative population sample in Greece).</p> <p>b. "Current daily e-cigarette use in the EU in 2017 was rare among former smokers of >10 years and was positively associated with recent (≤5 years) smoking cessation. Former daily e-cigarette use was also positively associated with recent (≤2 years) smoking cessation"</p> <p>Ref: Farsalinos , Barbouni 2020 Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries. http://dx.doi.org/10.1136/tobaccocontrol-2019-055190</p>	
388	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>Page 70</p> <p>To develop less harmful products is the best solution in the history of efforts to reduce the impact of smoking in society. While bans and measures by governments have reduced the effects of smoking by one percent, such a supply from below has reduced them by tens of percent. And many people abstain because of the fact that they have switched to substitution. We know from practice that most people get used to it when they start substitution treatment than when they go into abstinence treatment.</p>	Please see Table 1, answer 1.
			<p>The SCHEER opinion omits many publications on the role of electronic cigarette in the cessation of tobacco smoking. For example, studies by Lucchiari (2020) and Glasser (2020) which demonstrated that more frequent and stable use of electronic cigarettes can help smokers to quit smoking.</p> <p>Electronic cigarettes are also recommended as cessation help by the UK National Health Services website: Using e-cigarettes to stop smoking, and confirms that “Many thousands of people in the UK have already stopped smoking with the help of an e-cigarette. There's growing evidence that they can be effective.” (https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/).</p> <p>Lucchiari 2020 Benefits of e-cigarettes in smoking reduction and in pulmonary health among chronic smokers undergoing a lung cancer screening program at 6 months.</p>	Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

<https://www.sciencedirect.com/science/article/abs/pii/S0306460319301832?via%3Dihub>

Glasser, A., et al. (2020). "Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) Study." *Nicotine & Tobacco Research*. [https://www.unboundmedicine.com/medline/citation/32939555/Patterns_of_e-cigarette_use_and_subsequent_cigarette_smoking_cessation_over_two_years_\(2013/2014_to_2015/2016\)_in_the_Population_Assessment_of_Tobacco_and_Health_\(PATH\)_Study](https://www.unboundmedicine.com/medline/citation/32939555/Patterns_of_e-cigarette_use_and_subsequent_cigarette_smoking_cessation_over_two_years_(2013/2014_to_2015/2016)_in_the_Population_Assessment_of_Tobacco_and_Health_(PATH)_Study).

389	Juusela Maria, Doctors against tobacco (DAT) Finland, Finland	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>In Finland, there have been attempts over decades to reduce smoking, which is sustained by nicotine addiction. Nicotine containing electronic cigarettes promote and keep up nicotine addiction (Walley et al. 2019). Sale of such electronic cigarettes is clearly against the goal of reducing/ending smoking in Finland and in Europe (Timberlake et al. 2020).</p> <p>References Timberlake DS, Laitinen U, Kinnunen J, Rimpela AH. Strategies and barriers to achieving the goal of Finland's tobacco endgame. <i>Tob Control</i> 2020 Jul;29(4):398-404. doi: 10.1136/tobaccocontrol-2018-054779. Epub 2019 May 31. Walley SC, Wilson KM, Winickoff JP, Groner A. Public Health Crisis: Electronic Cigarettes, Vape, and JUUL. <i>J Pediatrics</i>. 2019, 143: e20182741. Ref: Timberlake et al (2019). Strategies and barriers to achieving the goal of Finland's tobacco endgame. <i>Tob Control</i> 2020;29:398-404. doi:10.1136/tobaccocontrol-2018-054779.</p>	Thank you for your comment.																		
390	Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania	6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use	<p>P70/</p> <table border="0"> <tr> <td>P</td> <td>71/</td> <td>L</td> <td>1</td> <td>-</td> <td>L36-41</td> </tr> <tr> <td>P</td> <td></td> <td>70/</td> <td>L</td> <td></td> <td>17</td> </tr> <tr> <td>P</td> <td>71/</td> <td>L19 – 28</td> <td></td> <td></td> <td>45</td> </tr> </table> <p> Role_of_electronic_cigarettes_in_the_cessa</p>	P	71/	L	1	-	L36-41	P		70/	L		17	P	71/	L19 – 28			45	Please see reply to comment 394.
P	71/	L	1	-	L36-41																	
P		70/	L		17																	
P	71/	L19 – 28			45																	
391	Human Delon, Physician, Unit	6.7 Role of electronic cigarettes in the	The Cochrane report has refuted the Preliminary Opinion's position, that there is weak evidence for the support of e-cigarettes' effectiveness in helping smokers to quit. The Opinion itself cites																			

	<p>ed Kingdom</p> <p>cessation of traditional tobacco smoking and dual use</p>	<p>two randomized controlled trials which clearly showed that e-cigarettes were more effective than NRTs [1,2]. We use NRT in practice for cessation, so it is incomprehensible that Scheer recognises this fact. Furthermore, the recently updated Cochrane review report recently analyzed a substantial 50 studies and concluded that is moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and compared to NRTs [3].</p> <p>1. Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. <i>Lancet Respir Med.</i> 2020 Jan;8(1):54-64. doi: 10.1016/S2213-2600(19)30269-2.</p> <p>2. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, Li J, Parrott S, Sasieni P, Dawkins L, Ross L, Goniewicz M, Wu Q, McRobbie HJ. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. <i>N Engl J Med.</i> 2019 Feb 14;380(7):629-637. doi: 10.1056/NEJMoa1808779.</p> <p>3. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. <i>Cochrane Database Syst Rev.</i> 2020 Oct 14;10:CD010216. doi: 10.1002/14651858.CD010216.pub4.</p>	<p>Please see Table 1, answer 11.</p>
<p>392</p> <p>Froguel Alizee, Cancer Research UK, United Kingdom</p>	<p>6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use</p>	<p>Cancer Research UK disagrees that there is only weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit.</p> <p>The 2016 Cochrane review referenced in the Committee's opinion showed initial signs that e-cigarettes may aid smoking cessation. However, since its publication in 2016, several further studies have demonstrated the effectiveness of e-cigarettes in smoking cessation. This includes a 2018 meta-analysis(1) and an English population-based study, which showed that individuals using an e-cigarette are around 60% more likely to quit smoking compared to using no aid or using over-the-counter nicotine replacement therapy(2)The 2019 Cancer Research UK-funded study referenced in the report also showed that using e-cigarettes in combination with behavioural support was nearly twice as effective as nicotine replacement therapy (NRT) and behavioural support.(3) Finally, the Cochrane review has also been updated in 2020, with evidence of the role of e-cigarettes in promoting smoking cessation now being reported with moderate certainty.(4)</p>	<p>Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.</p> <p>Please see also Table 1, answer 6.</p>

An analysis of population trends in England suggested that e-cigarettes may have helped an additional 18,000 people in England in 2015 to quit for the long term.(5)

Overall, Cancer Research UK believes there is moderate evidence to support the role of e-cigarettes in smoking cessation and strong evidence within the UK policy context specifically.

References:

1. Liu, X., Lu, W., Liao, S., Deng, Z., Zhang, Z., Liu, Y., & Lu, W. (2018). Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine*, 97(19), e0324.
2. Brown, J., Beard, E., Kotz, D., Michie, S., & West, R. (2014). Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction* (Abingdon, England), 109(9), 1531-40.
3. Hajek P, Phillips-Waller A, Przulj D et al. (2019) A randomised trial of e-cigarettes versus nicotine-replacement therapy. *New England Journal of medicine*.
4. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>
5. Beard E, West R, Michie S, Brown J. (2016) Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends *BMJ*; 354 :i4645

<p>393 Erkkila Brian,The Foundation for a Smoke-Free World,United States of America</p>	<p>6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use</p>	<p>P70L45-P70L51</p> <p>A more recent Cochrane review has found that there is moderate-certainty that quit rates are higher (RR 1.60; CI 1.25-2.27) among subjects randomized to nicotine electronic cigarettes when compared to those assigned to use nicotine replacement therapy (NRT) (Hartmann-Boyce, 2020). Further there was no evidence of a difference in risks for adverse events when compared to NRT. Nicotine containing electronic cigarettes were more effective than non-nicotine products in helping smokers quit (RR 1.69; CI 1.25-2.27).</p> <p>P71L33-34</p> <p>While more robust longitudinal data on the effect of electronic cigarettes on smoking cessation would be welcome it should be noted that the PATH study from the US FDA has provided some useful findings. In a multivariable-adjusted analyses, daily e-cigarette use at Wave 1 was associated with higher odds of smoking abstinence at both Waves 2 and 3 (AOR=1.77; CI 1.08-2.89) A recent study found that Increasing e-cigarette use across waves of</p>	<p>Please see Table 1, answer 6.</p> <p>Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.</p>
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the PATH study was associated with a nearly 3.4 times higher likelihood (Adjusted RRR: 3.38, p<0.001) of quitting smoking in the short term (<1yr) and 81% higher likelihood of sustained long term quitting (Adjusted RRR 1.81, p=0.02) compared with non-e-cigarette users. A sustained quit (>1yr) through the use of e-cigarettes was higher for daily smokers than it was for non-daily smokers. (Glasser, 2020).

Glasser, A., Vojjala, M., Cantrell, J., Levy, D. T., Giovenco, D. P., Abrams, D., & Niaura, R. (2020). Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) Study. *Nicotine & Tobacco Research*. September 2020. <https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntaa182/5906689?redirectedFrom=fulltext>
 Hartmann-Boyce_J, McRobbie_H, Lindson_N, Bullen_C, Begh_R, Theodoulou_A, Notley_C, Rigotti_NA, Turner_T, Butler_AR, Hajek_P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD010216. <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>
 Kalkhoran S, Chang Y, Rigotti NA. Electronic Cigarette Use and Cigarette Abstinence Over Two Years among U.S. Smokers in the Population Assessment of Tobacco and Health Study. *Nicotine Tobacco Res.* 22(5): 728-733

394 Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania

6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

n/a

National data from Member States and other countries where TPD is in force can also be used to consider relevant trends. Irish Government data from 2019 (attached) show smoking rates in the country have fallen from 23% in 2015 to 17% in 2019; concurrent with a rise in e-cigarette use from 3-5%. Less than 1% of non-smokers use e-cigarettes, according to the data.

P 70/ L 36 - 41

The Committee notes the use of electronic cigarettes as a cessation aid across the EU varies significantly across the Member States and the UK; citing the UK as having the highest rate of e-cigarette use in this context. It would help the report achieve its stated objective if it were to consider this in light of data on smoking rates across the Member States. In this regard, the UK - which has the highest level of e-cigarette use - has seen the largest fall in smoking prevalence according to Eurobarometer. In the UK, the prevalence of cigarette smoking fell from 22% (2015) to 17% (2017).

Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

P 71/ L 1 - 17
As has been correctly identified by the Committee, two randomized controlled trials have been published comparing the efficacy of e-cigarette use and nicotine replacement therapies (NRT). Both studies showed e-cigarettes to deliver significantly higher cessation rates than NRT, while the latter is approved for a quit indication based on a randomized control trial.

As two RCTs have shown conclusively that e-cigarettes are effective in smoking cessation, it seems absurd for the committee to conclude in the opinion taken in the scientific opinion, that the weight of evidence for smoking cessation is weak (P 19 L 1-2). The current evidence as reviewed by the committee is that e-cigarettes are associated with greater levels of cessation than nicotine replacement therapies.

P 70/ L 45
A new Cochrane review has been published following the opening of this consultation. Hartmann-Boyce (2020) concludes: "More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy"

P 71/ L19 - 28
The message from the UK Public Health authorities (2020) has been significantly at odds with that in the United States. For completeness, the view of Public Health England should be considered as per their latest evidence update: "data from stop smoking services in England suggests that when a vaping product is used in a quit attempt, either alone or with licensed medication, success rates are comparable to, if not higher than, licensed medication alone" It seems odd to quote US authorities without quoting those from the UK.

n/a
No consideration is given to the impact of non-traditional flavors on smoking cessation. There is data to suggest that the use of non-tobacco flavors and smoking cessation are correlated. These studies are attached.

Farsalinos et al found that dual users (those who both smoke and vape) were more likely to be using tobacco flavors (53%) than former smokers (43.1%); while former smokers preferred sweet (63.9%) and fruit (71.7%) flavored e-cigarettes.

Russell et al surveyed 22,411 US e-cigarette users, the majority of whom had given up smoking entirely. Results indicated that adults who had completely switched from smoking cigarettes to using e-cigarettes in the past 5 years are increasingly likely to have initiated e-cigarette use with products not flavored to taste like tobacco.

395 Arnott Deborah, A ction on Smoking and Health (UK), United Kingdom
6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

SCHEER concludes that there is weak evidence for the support of e-cigarettes effectiveness in helping smokers quit.

This is inconsistent with the most recent Cochrane systematic review published in October 2020 which concluded that there is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to nicotine replacement therapies (NRT). Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain.

<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>

This is an important finding as NRT is recognized by WHO as an 'essential medicine' because it has been shown to effectively promote smoking cessation in individuals.
https://www.who.int/tobacco/communications/highlights/note_nrt_therapy/en/

(NB I've included links as the files would not upload)

396 Notley Caitlin, Norwich Medical School, University of East
6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use

Work led by myself and undertaken by my research group indicates that e-cigarettes play an important role in smoking cessation for many. Critically the studies outlined below use mixed methods approaches to explore individual trajectories through quitting, suggesting that continued e-cigarette use may support not only smoking cessation attempts, but also long term smoking abstinence, by helping ex-smokers avoid relapse to tobacco smoking.

Please see table 1, answer 11.

In a qualitative study, we found overall that e-cigarettes were experienced as being a satisfying and acceptable harm reduction alternative to tobacco smoking. Initiating e-cigarette use was experienced as a revelation for some, who were quickly able to fully switch to using e-cigarettes rather than continuing to smoke tobacco. For others, periods of dual use or smoking relapse combined with attempts at vaping that were not initially satisfactory. Experimentation with different devices and different setups, over time, resulted in some ‘sliding’ rather than switching to vaping. E-cigarettes met the needs of some ex-smokers by substituting physical, psychological, social, cultural and identity-related aspects of tobacco addiction. Some vapers reported that they found vaping pleasurable and enjoyable—being more than a substitute but actually preferred, over time, to tobacco smoking. This clearly suggests that vaping is a viable long-term substitute for smoking.

Thank you for your comment.

Notley, C, Ward, E, Dawkins, L & Holland, R (2018) The unique contribution of e cigarettes for tobacco harm reduction in supporting smoking relapse prevention. *Harm Reduction Journal* 15:31
<https://doi.org/10.1186/s12954-018-0237-7>

In a longitudinal study we collected detailed subjective data over 12 months to assess trajectories of use and dual use over time. We found that a social context supportive of vaping was important to support e cigarette users to remain tobacco free. A dislike of the ‘vaping culture’ was expressed by some who had relapsed back to using tobacco. In this sample of UK e-cigarette users who report having used e-cigarettes to quit smoking, a social context that supports continued vaping was perceived to be helpful in preventing relapse to smoking.

Notley, C., Ward, E., Dawkins, L., and Holland, R. (2020) User pathways of e-cigarette use to support long term tobacco smoking relapse prevention: A qualitative analysis. *Addiction*.
<https://doi.org/10.1111/add.15226>.

In an online survey we found associations between device type and

nicotine strength e liquid used, suggesting that smokers need support to choose the right vaping set up in order to support a quit attempt and maintain tobacco smoking abstinence. Those using a tank or vape pen appeared less likely to relapse than those using a cig-a-like (tank vs. cig-a-like OR=0.06, 95% CI 0.01 to 0.64, p=0.019). There was an inverse association between starting self-reported e-cigarette liquid nicotine concentration and relapse, interacting with device type (OR=0.79, 95% CI 0.63 to 0.99, p=0.047), suggesting risk of relapse may have been greater if starting with a low e-cigarette liquid nicotine concentration and/or cig-a-like device.

Gentry, S, Ward, E, Dawkins, L, Holland R & Notley, C Reported patterns of vaping to support long-term abstinence from smoking: a cross-sectional survey of a convenience sample of vapers. Harm Reduction Journal

The recently update Cochrane review reports moderate-certainty evidence that e cigarettes with nicotine increase quit rates compared to e cigarettes without nicotine and compared to NRT. Hartmann-Boyce et al. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4

Ref:

Gentry et al (2020) Reported patterns of vaping to support long-term abstinence from smoking: a cross-sectional survey of a convenience sample of vapers.

Notley et al (2018). The unique contribution of e-cigarettes for tobacco harm reduction in supporting smoking relapse prevention. Harm Reduction Journal (2018) 15:31

Notley et al (2020). User pathways of e-cigarette use to support long term tobacco smoking relapse prevention: A qualitative analysis.

397 Goldberg Johann,Notley - Private contribution,France

ABSTRACT - Lines 49 to 52

The authors fail to examine vaping in the European context. There is a heavy reliance on US data yet relevant European data is ignored, despite the purpose of the Opinion being to report on the effectiveness of TPD2, which is a European directive.

Please see table 1, answer 8.

In France, one of the highest health authorities, the National Academy of Medicine, has published a press release in December 2019 to denounce the misconceptions about vaping, and specifically explains the reasons of the US crisis.

Hereafter a translation of that press release:
"TITLE : The National Academy of Medicine recalls the proven advantages and unduly alleged disadvantages of electronic cigarettes (vaping).
Confidence in vaping is now shaken by the observation of a sudden epidemic of pulmonary diseases localized in the United States, as well as by the World Health Organization (WHO) report, which qualifies electronic cigarettes 'unquestionably harmful', without any evidence. The position expressed by the National Academy of Medicine in 2015 advised to guarantee the safety of products, to declare the substances present in e-liquids and, above all, to prohibit their sale to minors as well as advertising and use where smoking is prohibited. This is the case nowadays in France where vaping falls under quality and safety standards, in opposition to what is happening in the United States presently.

Please see table 1, answer 11.

This crisis of confidence could kill thousands of smokers, since tobacco kills half of their loyal consumers. One should not confuse the container with the toxicity of the contents.

The American epidemic of pulmonary attacks is due to a diversion of the electronic cigarette use since, after accusing vaping itself, the Center for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) recognize that this diversion is the main cause of this epidemic concerning nearly 2,200 people with 42 deaths in 4 months. One must not wrongly accuse the container (the electronic cigarette) of being harmful, when actually the cause for the US alert is the harmful content.

Electronic cigarettes, which are less dangerous than cigarettes, help to quit and reduce tobacco consumption. 700,000 smokers have quit thanks to vaping.

Please see table 1, answer 1.

It is established that vaping is less dangerous than the cigarette: as expressed by the National Academy of Medicine since 2015, it is preferable for a smoker to vape. Since 2016, the High Authority for Health (HAS) considers vaping 'as an aid to stop or reduce the consumption of tobacco for smokers', sometimes better than other

nicotine substitutes, as proven in a randomized trial. The institution 'Public Health France' indicates that at least 700,000 people have quit smoking thanks to vaping. Though the concern is well founded in the USA, this is not what one can observe in France: studies by 'Paris Without Tobacco' show that the overall nicotine consumption by young people - vape plus tobacco - decreases thanks to French and European regulations.

The epidemic caused by the youngsters' misuse of the electronic cigarette reminds Americans that they have insufficiently regulated its use. This lack of regulation explains this crisis, like the one of opioids. In France, we strongly advise that every smoker who is thinking of quitting by using a electronic cigarette should not hesitate and vape, since the High Authority for Health (HAS) has made it a useful product for smoking cessation and that has been proven to work.

The National Academy of Medicine warns that one must be careful not to take aim at the wrong target! " Original article: <http://www.academie-medecine.fr/lacademie-nationale-de-medecine-rappelle-les-avantages-prouves-et-les-inconvenients-indument-allegues-de-la-cigarette-electronique-vaporette/>

398	Bouchard Kévin,Aid uce,France	ABSTRACT	Line 13 et 14: “Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes”.	Please see table 1, answer 1.
			Line 42-44: “Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes”. “Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco”. “These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking”.	Please see table 1, answers 5, 6, 7.

“Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect”. While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance”.

Line 49-51: “E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support”. “Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping”.

399 maistre ABSTRACT
cédric,priv
ate
citizen,Fra
nce

Abstract: lines 13 and 14: this part indicates that the risks of cardiovascular problems due to vaping are high.

Please see table 1, answer1.

However, a 2014 study, which aimed to compare the “potential risks of using electronic cigarettes, against the well-established devastating effects of smoking” explains in its findings that the currently available evidence indicates that “cigarettes electronic cigarettes are by far a less harmful alternative to smoking” and that “significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes”.

Abstract: lines 42 to 44: These lines note that vaping is a gateway to smoking.

Please see table 1, answers 5, 6, 7.

However, many scientific studies have already shown that no, vaping does not lead to smoking. (Study n ° 1 [2020], study n ° 2 [2016], study n ° 3 [2014], study n ° 4 [2019], study n ° 5 [2018]).

Study 1 concludes that there is "no evidence of an increased risk of transitioning to daily smoking at age 17 in smokers who have ever smoked and who have also experimented with e-cigarettes."

Study 2 reports that "two-thirds of exclusive e-cigarette users in the past 30 days have used tobacco."

The 3rd explains that her data "does not suggest that the E-cig can facilitate smoking and suggests that it is rather widely used to quit smoking."

Work # 4 states in its findings that "data from five youth surveys in the US and UK show (...) the lack of a significant bridging effect."

Research # 5 explains that "although the trial of e-cigarettes may lead to an increase in smoking among some young people, the overall population-level effect appears negligible given the reduction in the number of smokers over the period of time. 'increase in vaping'.

Abstract: lines 49 to 51: Finally, this part indicates that there is only weak evidence that vaping helps to quit smoking.

These conclusions contradict the results of several studies (study n ° 1 [2019], study n ° 2 [2017]), which have already proven that the use of an electronic cigarette increases the chances of to quit smoking.

Study # 1 shows that "electronic cigarettes are more effective in quitting smoking than nicotine replacement therapy, when both products are accompanied by behavioral support."
Study # 2 notes in its findings that "almost everyone smoked before they started vaping. A large majority of them agreed that unlike other smoking cessation aids, they can quit smoking through vaping."

(Sorry for using Google translate)

400 matthias ABSTRACT
dunac,none
,France

49/51 Je suis un ancien fumeur de plus de 1 paquet de cigarettes par jour, j'ai arrêté le tabac GRACE à la cigarette électronique. Dans mon entourage nous sommes plus de 50% a avoir fait un arrêt du tabac avec la e-cigarette, de nombreuses études scientifiques vont déjà dans le sens que la cigarette électronique est un moyen avec plus de réussite pour un arrêt du tabac comparé aux dispositifs tels

Thank you for your comment.

401	Furlotti Luigi, Vaper, Italy	ABSTRACT	<p>que patch, nicorettes... Toutes vos conclusions sont mensongères et dirigées par des lobbies très puissants au sein de votre institution.</p> <p>Good Morning, I'm a Vaper for over ten years. I don't use cigarettes anymore. I've recently done ultrasounds, tactics and magnetic resonations and it seems I've never smoked. In reality I've smoked from the age of 13 to 50. Now I'm 61 years old.</p>	Thank you for your comment.
402	No agreement to disclose personal data	ABSTRACT	<p>lines 13 to 14</p> <p>Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.</p> <p>lines 42 to 44</p> <p>Cependant, de très nombreux travaux scientifiques ont d'ores et déjà démontré que non, vapoter ne conduit pas à fumer. (https://www.sciencedirect.com/science/article/pii/S0376871620300181?fbclid=IwAR2iIQx_ZKenOO9KB39OMchLpW4ImsRcHk-wwlCqEec6gxXj-zelcH3AKck [2020], https://academic.oup.com/ntr/article/19/11/1345/2738979 [2016], http://beh.santepubliquefrance.fr/beh/2016/15/2016_15_2.html [2014], étude n°4 [2019], https://tobaccocontrol.bmj.com/content/28/6/629?fbclid=IwAR3vQuMwyrFa6sHDFU-jOGj82D318LxuZYUcJzT-UdWK05S-RzH8qFoeheo&utm_campaign=tc&utm_content=consumer&utm_medium=cpc&utm_source=trendmd&utm_term=usage-042019 [2018]).</p> <p>L'étude n°1 conclut qu'il n'y a « aucune preuve d'un risque accru de transition vers le tabagisme quotidien à 17 ans chez les fumeurs ayant déjà fumé et ayant également expérimenté les e-cigarettes .</p> <p>L'étude n°2 indique que « les deux tiers des utilisateurs de cigarettes électroniques exclusives des 30 derniers jours ont déjà consommé du tabac ».</p> <p>La troisième explique que ses données « ne suggèrent pas que la E-cig puisse faciliter le passage au tabac et suggèrent qu'elle est plutôt largement utilisée pour arrêter de fumer ».</p>	Please see table 1, answer 1.

Le travail n°4 indique dans ses conclusions que « les données de cinq enquêtes menées auprès des jeunes aux États-Unis et au Royaume-Uni montrent (...) l'absence d'un effet de passerelle important ».

Enfin, la recherche n°5 explique que « bien que l'essai de cigarettes électroniques puisse entraîner une augmentation du tabagisme chez certains jeunes, l'effet global au niveau de la population semble négligeable compte tenu de la réduction du nombre de fumeurs pendant la période d'augmentation du vapotage ».

lines 49 to 51
Enfin, cette partie indique qu'il n'existe que de faibles preuves que vapoter aide à arrêter de fumer.

Des conclusions qui entrent en contradiction avec les résultats de plusieurs études (https://www.nejm.org/doi/full/10.1056/NEJMoa1808779?query=fatured_home [2019], <https://www.mdpi.com/1660-4601/14/7/798> [2017]), ayant d'ores et déjà prouvé que l'utilisation d'une cigarette électronique augmente les chances de se sevrer du tabagisme.

L'étude n°1 démontre que « les cigarettes électroniques sont plus efficaces pour arrêter de fumer que la thérapie de remplacement de la nicotine, lorsque les deux produits sont accompagnés d'un soutien comportemental ».

L'étude n°2 note dans ses conclusions que « presque tout le monde fumait avant de commencer à vapoter. Une grande majorité d'entre eux ont reconnu que, contrairement aux autres aides à l'arrêt du tabac, ils pouvaient arrêter de fumer grâce au vapotage ».

403	Mayer Bernhard-Michael, Pharmacy & Toxicology, University	ABSTRACT	<p>lines 13-14 Epidemiological studies show that nicotine consumption doesn't increase cardiovascular risk [1,2]. The impaired blood vessel function of smokers is fully reversed one month after switching to vaping with or without nicotine [3].</p> <p>lines 15-19 If at all, N-nitrosamines are present only in trace amounts in e-</p>	<p>The SCHEER argues that 'most of the cardiovascular effects demonstrated in humans are consistent with the known sympathomimetic effects of nicotine'(Section 6.5.4), opposing the view that combustion products are mostly responsible</p> <p>Please see Table 1, answer 4.</p>
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cigarette emissions, excluding cancerogenic effects of the inhaled aerosols (see [4] and references therein). Based on over 100 published emission analyses, the lifetime cancer risk of vaping was calculated as two orders of magnitude lower than smoking [5].

lines 20-21
I assume the SCHEER refers to the outgassing of defective or overloaded batteries. Such accidents occur at much higher frequency with many other battery-driven devices, including smartphones and laptops.

lines 30-37
Published data on e-cigarette vapor effects on indoor air quality unequivocally demonstrate that the air concentrations of potential toxicants are far below the accepted thresholds after unrestricted vaping in closed rooms [6-11].

lines 42-47
Epidemiological studies show an association of vaping with smoking due to common liabilities, i.e., teenagers inclined to risky behavior are tempted to try all kinds of dangerous things, including tobacco and electronic cigarettes. Continuously decreasing smoking rates among minors in Europe dismiss the gateway claim.

lines 49-52
Millions of smokers became non-smokers by switching to vaping. In most European countries, e-cigarettes are the most frequent cessation aid used by smokers. Therefore, the evidence that e-cigarettes help smokers to either quit or substantially reduce smoking is strong.

Due to limited file size, only 4 out of 11 cited papers are attached (#2, #3, #9, and

Small amounts of impurities may be present even in the pharmaceutical grade nicotine.

The SCHEER is very clear and precise '...For both poisoning and injuries due to burns and explosion, the evidence for the intrinsic capability to cause health problems is strong, but the incidence is quite low: only few case reports are available '

Two issues are clearly stated:

- It is noted that burns and explosions are a realistic health concern there is clear evidence from studies
 - The incidence is quite low meaning that the frequency is very low
- The mandate of the Opinion is not to compare with other types of electronic devices and/or other types of cigarettes.

Please see table 1, answer 4.

Please see table 1, answer 5, 6, 7.

Thank you for your comment. The SCHEER sufficiently underpinned the conclusion.

			#11). 1. Mills et al. Circulation 129, 28-41 (2014) 2. Benowitz et al. JAMA Intern. Med. 178, 622-631 (2018) 3. George et al. J. Am. Coll. Cardiol. 74, 3112-3120 (2019) 4. Belushkin et al. Chem. Res. Toxicol. 33, 657-668 (2020) 5. Stephens. Tob. Control 27, 10-17 (2018) 6. McAuley et al. Inhal. Toxicol. 24, 850-857 (2012) 7. O'Connell et al. Int. J. Environ. Res. Public Health 12, 4889-4907 (2015) 8. Logue et al. Environ. Sci. Technol. 51, 9271-9279 (2017) 9. Liu et al. Int. J. Environ. Res. Public Health 14, 969 (2017) 10. van Drooge et al. Environ. Sci. Pollut. Res. 26, 4654-4666 (2019) 11. Schober et al. Int. J. Hyg. Environ. Health 222, 486-493 (2019)	
404	Scalise Mario,Privato cittadino,Italy	ABSTRACT	Il presidente dell'associazione ANPVU vi ha mandato 1200 studi che contraddicono il parere di Scheer	Thank you for your comment.
405	Visentini Alessandro ,Il mio angolo dello svapo ,Italy	ABSTRACT	Questo settore ha salvato la mia vita, e molte altre. È da 6 anni che svapo, non ho mai avuto problemi da quando uso la sigaretta elettronica . Sia sotto il profilo della salute che sotto il profilo sportivo, questo è un settore che potrebbe ridurre notevolmente i tumore provocati dal fumo. Sono sicuro che ci siano prodotti simili ma nettamente più dannosi per la salute, prodotti meno dannosi delle sigarette elettroniche non li troverete mai, ci sono svariate prove scientifiche che lo dimostrano. Moltissimi luminare come Veronesi le hanno citate come il mgior metodo ler smettere di fumare.	Thank you for your comment.
406	Abate Giuliano,ww.fumon egliocchi.it ,Italy	ABSTRACT	lines 13 and 14 : this part indicates that the risks of cardiovascular problems due to vaporisation are high. However, this study https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/ which aimed to compare the "potential risks of using e-cigarettes with the well-established devastating effects of smoking" explains in its results that the currently available evidence indicates that : "Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes"	The Opinion has been revised accordingly.

407	GOLINVA ABSTRACT UX Benjamin,(Private individual) ,Belgium	<p>1) Lines 13 and 14, in the abstract. your conclusion states "the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong." However, in Farsalinos[2014], we can read, in the conclusions: "“Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes”". Farsalinos[2014]: Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. <i>Ther Adv Drug Saf.</i> 2014;5(2):67-86. doi:10.1177/2042098614524430</p> <p>2) Lines 42 and 44 : "Regarding the role of electronic cigarettes as a gateway to smoking/the initiation of smoking particularly for young people, the SCHEER concludes that there is strong evidence that electronic cigarettes are a gateway to smoking for young people. "</p> <p>Numerous studies have show that this statement is simply not true: In the study linked at https://doi.org/10.1016/j.drugalcdep.2020.107853 : “Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes”. In the study linked at https://doi.org/10.1093/ntr/ntw388 : “Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco”. In the study linked at http://invs.santepubliquefrance.fr/beh/2016/15/2016_15_2.html: “These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking”. Coombs[2018] : “Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect”. Levy[2019] : “While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance”. Coombs[2018]: Lee PN, Coombs KJ, Afolalu EF. Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review. <i>F1000Res.</i> 2018;7:1915. Published 2018 Dec 10. doi:10.12688/f1000research.16928.3 Levy[2019] : Levy DT, Warner KE, Cummings KM, et al , Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check, <i>Tobacco Control</i> 2019;28:629-635.</p>	<p>The Opinion has been revised accordingly.</p> <p>Please see table 1, answer 1.</p> <p>Please see table 1, answer 5.</p>
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408 Albrecht
Hans-
Peter,
Interesseng
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IG ED,
Germany

ABSTRACT

As a consumer of vapour products for 4,5 years exclusively instead of combusted tobacco (for 35 years) I would kindly ask you to take my following comments into consideration. After reading the report in detail I find that the conclusions made in the abstract do not correctly mirror the contents/data in the report further down. It appears to be strongly biased and seems to be meant to encourage policymakers to pursue burdensome restrictions on (adult) consumers ignoring unintended consequences. To me, what the report lacks is adequate and “real-life-proven” advice for policymakers. ll. 42-44:
Given the fact that the so called “Gateway-Theory” has been tried again and again (but hasn’t been substantiated, and has been debunked repeatedly, e.g. through confounding), I can’t see how SCHEER concludes that there is “strong” evidence - in fact there seems to be little to no evidence
Source: National Health Interview Survey, 2014–2018 data. <https://www.cdc.gov/nchs/nhis.htm>:

Please see table 1, answer 2 and chapter 4 in the Opinion.

Please see table 1, answer 5.

During the time period studied (2014-2018), smoking by young adults aged 18-24 fell by ~50%. They can't even pretend there is a meaningful gateway effect. And all this data is from pre-„Tobacco21“ being federal law. Regarding a gateway in the light of accelerated reduced smoking rates among youths and by applying common sense the direction (gateway) rather is from smoking to vaping.
common liability CLA vs Gateway hypothese GH
Hintergrund: Zwei konkurrierende Konzepte befassen sich mit der Entwicklung des Umgangs mit psychoaktiven Substanzen: die "Gateway-Hypothese" (GH) und die Common Liability to Addiction (CLA). Die Methode: Die Literatur zu theoretischen Grundlagen und empirischen Erkenntnissen zu beiden Konzepten wird gesichtet. Ergebnisse: Die Daten deuten darauf hin, dass die Sequenzierung des Einstiegs in den Drogenkonsum, das Kernelement von GH, eher variabel und opportunistisch als einheitlich und entwicklungs-deterministisch ist. Der Zusammenhang zwischen den Risiken des Konsums verschiedener Substanzen lässt sich, wenn überhaupt, leichter durch gemeinsame Grundlagen als durch eine spezifische Staffelung erklären. Im Gegensatz dazu beruht das CLA-Konzept auf der genetischen Theorie und wird durch Daten gestützt, die gemeinsame Quellen der Variation des Risikos für bestimmte Abhängigkeiten identifizieren.

Übersetzt mit www.DeepL.com/Translator (kostenlose Version)

Common liability to addiction and “gateway hypothesis”: Theoretical, empirical and evolutionary perspective:

Abstract

Background: Two competing concepts address the development of involvement with psychoactive substances: the “gateway hypothesis” (GH) and common liability to addiction (CLA). Method: The literature on theoretical foundations and empirical findings related to both concepts is reviewed. Results: The data suggest that drug use initiation sequencing, the core GH element, is variable and opportunistic rather than uniform and developmentally deterministic. The association between risks for use of different substances, if any, can be more readily explained by common underpinnings than by specific staging. In contrast, the CLA concept is grounded in genetic theory and supported by data identifying common sources of variation in the risk for specific addictions. This commonality has identifiable neurobiological substrate and plausible evolutionary explanations. Conclusions: Whereas the “gateway” hypothesis does not specify mechanistic connections between “stages”, and does not extend to the risks for addictions, the concept of common liability to addictions incorporates sequencing of drug use initiation as well as extends to related addictions and their severity, provides a parsimonious explanation of substance use and addiction co-occurrence, and establishes a theoretical and empirical foundation to research in etiology, quantitative risk and severity measurement, as well as targeted non-drug-specific prevention and early intervention. (PsycINFO Database Record (c) 2018 APA, all rights reserved)

(ca. 1400 Zeichen)

Common liability to addiction and “gateway hypothesis”: Theoretical, empirical and evolutionary perspective.

Journal Article COMMON_LABEL.DATABASE: APA PsycInfo

Vanyukov, Michael M. Tarter, Ralph E. Kirillova, Galina P. Kirisci, Levent Reynolds, Maureen D. Kreek, Mary Jeanne Conway, Kevin P. Maher, Brion S. Iacono, William G. Bierut, Laura Neale, Michael C. Clark, Duncan B. Ridenour, Ty A.

<https://psycnet.apa.org/record/2012-19516-002>

409 Julien Lemarchand, Clopinette Mérygnac, France

ABSTRACT

Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes.

Please see table 1, answer 1.

E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support. Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they

Please see table 1, answer 6.

		<p>started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping.</p>	
<p>410</p>	<p>Brown Jamie, Univ ersity College London, Un ited Kingdom</p>	<p>ABSTRACT</p> <p>Thank you for the opportunity to comment on an important and detailed review. I have focused only on smoking cessation as it is the area on which I have the greatest expertise and experience.</p> <p>Re: lines 49-51 on smoking cessation, crucially a new Cochrane review has been released with searches up to date until January 2020. It is now a living review and will be updated monthly from December 2020. The main conclusion is that: “there is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain.” The review also finds that “data from non-randomized studies were consistent with RCT data”.</p> <p>The new Cochrane review aligns with but updates the conclusions of the 2018 US National Academies of Science, Engineering, and Medicine Consensus Report (NASEM 2018) which concluded that there was “limited evidence that e-cigarettes may be effective aids to promote smoking cessation” primarily due to the large RCT published in NEJM since the NASEM review.</p> <p>It is important to note that the Surgeon General report and a draft of the US Preventive Services Task Force Draft Recommendation Statement and Draft Evidence Review: Interventions for Tobacco Smoking Cessation in Adults, Including Pregnant Persons were published prior to this latest Cochrane review. Cochrane reviews are widely regarded as gold-standard and independent evidence reviews to inform healthcare decision-making.</p> <p>We have published a number of articles using observational data from England, which are not cited but are relevant to forming a judgment on the impact of e-cigarettes on smoking cessation in England. I include the number of citations listed in Scopus to provide an indication of the influence they have had on the field: Brown, J., Beard, E., Kotz, D., Michie, S., West, R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: A cross-sectional population study <i>Addiction</i>, 2014, 109(9), pp. 1531-1540; Cited by 298</p>	<p>Thank you for your comment, relevant Cochrane studies have been considered in the Opinion.</p>

Hitchman, S.C., Brose, L.S., Brown, J., Robson, D., McNeill, A. Associations between E-Cigarette type, frequency of use, and quitting smoking: Findings from a longitudinal online panel survey in Great Britain. *Nicotine and Tobacco Research*, 2015, 17(10), pp. 1187-1194; Cited by 162

Brose, L.S., Hitchman, S.C., Brown, J., West, R., McNeill, A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction*, 2015, 110(7), pp. 1160-1168. Cited by 150

Beard, E., West, R., Michie, S., Brown, J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ (Clinical research ed.)*, 2016, 354, pp. i4645. Cited by 130

Jackson, S.E., Kotz, D., West, R., Brown, J. Moderators of real-world effectiveness of smoking cessation aids: a population study. *Addiction*, 2019, 114(9), pp. 1627-1638. Cited by 18 (published 2019).

Beard, E., West, R., Michie, S., Brown, J. Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017. *Addiction*, 2020, 115(5), pp. 961-974. Cited by 10 (published 2020).

Levy, D. T., Sánchez-Romero, L. M., Li, Y., Yuan, Z., Travis, N., Jarvis, M. J., Brown, J., and McNeill, A. (2020) England SimSmoke: the impact of nicotine vaping on smoking prevalence and smoking-attributable deaths in England. *Addiction*, <https://doi.org/10.1111/add.15269>. Uncited (published online Sept 2020).

411	Brown Jamie, University College London, United Kingdom	ABSTRACT	There is an apparent contrast in grading the strength of evidence. The report accepts cohort studies as providing strong evidence that electronic cigarettes are a gateway to smoking for young people; yet it regards RCT evidence (and unreviewed observational studies, both cohorts and time-series) as insufficient that e-cigarettes can help adults to quit. Even before the publication of the updated Cochrane review in Oct 2020, it would be helpful to be more explicit in the methods as to how different evidence bases can be graded so differently.	This cannot be concluded from the Abstract, please read the full Opinion.
412	Nathalie Darge, Tobacco Europe AISBL, Belgium	ABSTRACT	The SCHEER Preliminary Opinion fails to address the potential health benefits for millions of EU adult smokers using e-cigarettes as alternatives to smoking, ignoring the public health principle of tobacco harm reduction. SCHEER fails to address the opinion's terms of reference, to address individual and population public health considerations, and overlooks the required scientific analysis to help the Commission assess the potential need for legislative amendments under the Tobacco Products Directive. SCHEER state that e-cigarettes have negative impacts on health but does not position these harms in comparison to cigarettes. SCHEER	Please see table 1, answer 1.

disregards a growing body of international, independent scientific evidence that indicates exclusive e-cigarette use reduces users' exposure to toxicants and an effective component of tobacco harm reduction helping smokers to quit.

SCHEER's selective evidence fails to meet the required standards set out in its Rules of Procedure, including requirements of transparency and consideration of the best available scientific evidence.

Please see table 1, answer 2.

LN13-14 "the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong" is inconsistent with available evidence. There is strong supportive evidence of cardiovascular improvements when adult smokers switch to e-cigarettes (relative risks), and no increased cardiovascular risk of nicotine exposure in consumers who have no underlying cardiovascular pathology. SCHEER derive conclusions by reviewing limited and older studies, mistakenly inferring short-term, transient effects with longer-term outcomes supported by misleadingly and unscientifically assuming e-cigarette effects are comparable with those of cigarettes. A significant amount of scientific literature on the cardiovascular effects of e-cigarettes was omitted. This statement should be reconsidered to reflect the current scientific evidence.

The Opinion has been revised accordingly.

LN42-44 "there is strong evidence that electronic cigarettes are a gateway to smoking for young people" is inconsistent with evidence presented in available studies. A number of experts have concluded that these studies fail to provide evidence to support a direct association between e-cigarette use and resulting cigarette smoking or to define how to test the gateway theory. Many comprehensive reviews and studies have also criticised e-cigarette 'gateway' arguments and conclude that there is no reliable evidence of a gateway effect, with ASH UK recently finding youth smoking rates at an all-time low. This statement should be reconsidered to reflect a more comprehensive review of the literature.

Please see table 1, answer 5.

LN50-52 "there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit" is inconsistent

Please see table 1, answer 6.

with scientific evidence. While e-cigarettes are not medicinal smoking cessation devices, evidence from a number of studies not considered by SCHEER, shows that millions of EU and other smokers have successfully switched to e-cigarettes. The 2020 Cochrane Review evaluated the effect and safety of using e-cigarettes to help smokers achieve long-term smoking abstinence. Based on the scientific literature this statement should be reconsidered, and evidence should not be ‘weak’.

We respectfully urge SCHEER to review their conclusions and to transparently explain the analysis. The selective analysis, omission of the latest scientific evidence, and lack of transparency assessing the evidence does not meet the Committee’s own standards and the Opinion’s terms of reference. We support regulation grounded in science, considering objectively all evidence at hand and recognizing tobacco harm reduction to provide adult smokers who would otherwise continue to smoke the option of potentially less harmful nicotine products.

413 Hajek
Peter, Tobacco
Dependence
Research
Unit,
Wolfson
Institute of
Preventive
medicine,
QMUL, United
Kingdom

ABSTRACT Lines 7-28, the section on health effects:

E-cigarette use (vaping) is a replacement for smoking. Comparing health effects of vaping with those of smoking is the key issue of interest. The fact that this is absent from this document makes it much less useful.

The report is also marred by a significant problem with appraising the importance of different sources of evidence. Data from human studies, and especially epidemiological data, provide much stronger evidence than in-vitro studies, but this is ignored. E.g. imagine that trace levels of carcinogens are detected in, say, coffee, but coffee drinkers have no elevated systemic levels, and no excess cancer. The conclusion should be that coffee poses no cancer risk, rather than that there is ‘moderate evidence’ for this risk, because of the irrelevant in-vitro results. Yet this is the approach the authors used. Undue emphasis is put on in-vitro data that can be presented as signalling risks, while human intake and epidemiological data that show that the levels detected in vitro are immaterial are ignored.

For instance, data on Swedish snus users and long-term users of

Please see table 1, answer 1.

For human data and epidemiological studies see 6.5.4. These data are part of the overall assessment.

NRT suggest that nicotine has minimal long-term effects on the cardiovascular system – in the direct contradiction to the claim here that evidence of such risk from nicotine in e-cigarettes is strong. Evidence for cancer risk from systemic carcinogen levels in vapers is none, rather than ‘weak to moderate’. The claim that there is evidence that even second-hand exposure poses CVD and cancer risks is particularly tendentious. (It seems to be based on a finding of negligible cotinine levels (Ballbe 2014, Flouris 2013) and a project protocol with no data (Shearston 2019) – page 51, lines 35-42).

The Opinion has been revised accordingly.

Lines 42 – 47, the section on the ‘gateway effect’: The verdict is based exclusively on findings that the same young people try both products. This does not show causality. Much more important epidemiological data, that the authors did not include, show that the rise of vaping experimentation among adolescents has been accompanied by a decline, not an increase, in smoking. The authors’ conclusion is thus not just an inaccurate reflection of the existing evidence, but the opposite to what the evidence suggests.

Please see table 1, answer 5.

Lines 49-52, the section on treatment effects: The verdict here is also misleading. Randomised controlled trials (e.g. see the new Cochrane review), cohort and epidemiological studies looking at quit rates in people using different quitting methods, and use of quitting methods among ex-smokers, e.g. in Eurobarometer data, all indicate that e-cigarettes are helping smokers quit. The review does not include most of this literature and under-estimates the strength of the converging evidence.

Overall, the document is not an objective evaluation of evidence. As a guide to policy makers, it offers guidance that is mostly misleading and that, if followed, will favour cigarettes over less risky alternatives and have a negative effect on public health.

414 Carbonara Giovanni, ANPVU,Italy

ABSTRACT

Nicotine produces minor cardiovascular events but not major ones. CV risk in smoking comes from CO, not nicotine. "Snus delivers a high dose of nicotine with possible hemodynamic effects, but its impact on cardiovascular morbidity and mortality is uncertain." And

Based on its assessment, the SCHEER concludes that the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is moderate.

415	Loucas Nancy,Coa lition of Asia Pacific Tobacco Harm Reduction Advocates, New Zealand	ABSTRACT	<p>"toxic components other than nicotine appear implicated in the pathophysiology of smoking related ischemic heart disease."</p> <p>The members of CAPHRA posit that it is difficult to assess the "gateway theory" as it relates to a pathway between vaping and smoking. Even if it were to exist, it would have little effect on smoking prevalence. There are no available evidence that the increase in e cigarette use has increased the use of combustible tobacco. According to Lee (Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review (Lee, Coombs and Afolalu, 2019) the decline in youth smoking appears to have accelerated.</p> <p>Indeed, Chan, et al (Gateway or common liability? A systematic review and meta-analysis of studies of adolescent e-cigarette use and future smoking initiation (Chan et al., 2020) statement that "there is a longitudinal association between adolescent vaping and smoking initiation; however, the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders."</p>	Please see table 1, answer 5.
416	Martinez Javier ,JT International SA,Switzerland	ABSTRACT	<p>P.2, 1.13.14 The statement, "the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong" is inconsistent with the evidence presented in available studies. Based on the scientific studies available, the evidence should not be qualified as "strong". To date, the evidence for effects of e-cigarettes on long-term cardiovascular health in adult smokers who have switched to e-cigarettes is inconclusive. SCHEER omitted a significant amount of the scientific literature regarding the cardiovascular effects of e-cigarettes. The limited and selected studies described under section 6.5.4 do not provide an accurate assessment of the literature. For instance, D'Amario et al. 2019 notes that the effects of substances at the dose of exposure delivered by e-cigarettes remains the subject of several ongoing studies. The authors caution, "most of the data on the cardiovascular effects of electronic cigarettes are derived from preclinical, cross-sectional or small-sized clinical studies in which standard cigarettes were used as a comparison arm, thus providing limiting and conflicting results. A large majority of such studies were also not designed to infer causality. Furthermore, most of these studies focused on the acute effects of electronic cigarette exposure, whereas it is unknown how and if these effects would translate to chronic and longitudinal electronic cigarette use. Likewise, population-wide studies have been confounded by combustible cigarette use, thus making the effect of electronic cigarettes alone challenging for</p>	The Opinion has been revised accordingly.

interpretation.” The authors observed, “While some studies suggest that electronic cigarettes use might be associated with endothelial dysfunction, impaired platelet function and increased risk of adverse clinical events, other studies did not confirm these findings and epidemiological data mostly suggest that the use of electronic cigarettes appears to be safer than that of traditional tobacco cigarette.” Please refer to our comments provided under section 6.5.4 p.47, 1.27 onwards and under section scientific opinion P.15, 1.1-14. Please amend the text to reflect a more comprehensive review of the literature and consider separating absolute risk for never smokers from relative risk for adult smokers with respect to cardiovascular measures.

P.2, 1.43-44 Please revise the statement: “there is strong evidence that electronic cigarettes are a gateway to smoking for young people.” SCHEER interpretation of the evidence to support and qualify that vaping serves as a “strong” gateway to smoking is not sound. Based on the scientific studies available and national smoking prevalence data in Member States, the evidence should not be qualified and reported as “strong”. Please refer to our extensive comment and additional scientific studies provided in relation to P.67, 1.26 onwards. Please amend this statement.

Please see table 1, answer 5

P.2, L.50-51 Please revise the statement, “SCHEER concludes that there is weak evidence for the support of electronic cigarettes effectiveness in helping smokers to quit.” Based on the scientific literature available, the evidence should not be qualified and reported as “weak”. The most recent Cochrane Review document contradicts SCHEER conclusion, pointing out, “we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT.” (Hartmann-Boyce et al. 2020). The review concludes, “Nicotine e-cigarettes probably do help people to stop smoking for at least six months” adding, “None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use.” Please also refer to our extensive comments and additional scientific studies provided under section 6.7 P.70, 1.19-28
 Ref:
 D’Amario (2019) Electronic Cigarettes and Cardiovascular Risk: Caution Waiting for Evidence
 Hartmann-Boyce J (2020) Electronic cigarettes for smoking cessation (Review)

Please see table 1, answer 6.

417 Landl ABSTRACT
 Michael,W
 orld
 Vapers'

Page 2, lines 42 - 47: Continuously decreasing smoking rates among adults and minors in Europe dismiss the gateway claim. It is well established [1] that adolescents who were less satisfied with their life, in general, were more likely to seek risky experiences and

Please see table 1, answer 5.

Alliance ,Austria		<p>have a higher tendency to use illicit substances regularly. As such, e-cigarettes are not a gateway for smoking, but rather bad circumstances in teenagers' lives lead to all kinds of risky behaviour. Therefore, lawmakers should focus on solving those problems and not use the gateway argument to limit access to vaping products for responsible adult consumers.</p> <p>Page 2, Lines 49 - 52: Millions of former smokers became non-smokers due to vaping. The correlation between the introduction and the higher popularity of vaping and declining smoking rates suggests that vaping is an important innovation to help people quit smoking. The 2018 U.S. National Academies of Sciences, Engineering, and Medicine Report [2] found that the smoking rate has decreased overall more rapidly since vaping became more prominent in the United States. There is no reason to suggest this would be different in Europe.</p> <p>References: [1] Kevin Tan, Jordan P. Davis, Douglas C. Smith & Wang Yang (2020) Individual, Family, and School Correlates across Patterns of High School Poly-substance Use, Substance Use & Misuse; [2] Levy DT, Warner KE, Cummings KM, et al Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check Tobacco Control 2019;28:629-635.</p>	Please see table 1, answer 6.
418 Needle Clive, EuroHealt hNet, Belgium	ABSTRACT	<p>Thank you for the Opinion and opportunity to comment. EuroHealthNet can welcome this evidence based Preliminary Opinion and the potentially important implications it has for effective regulatory development in the EU. In particular we note and concur with findings that</p> <ul style="list-style-type: none"> - Electronic cigarettes are relatively new in terms of exposure to humans. More research is needed, in particular on long-term health effects. In addition, while we note that some disaggregated evidence is reported, mainly in terms of age related issues and primarily among children and adolescents, we would welcome further consideration of equity related aspects in terms of health equity impact assessments, to help understand better the impacts on health inequalities. - Regarding the role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people, there is strong evidence that electronic cigarettes are a gateway to 	Thank you for your comment.

smoking for young people.

- There is also strong evidence that nicotine in e-liquids is implicated in the development of addiction and that flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation. Again in terms of potential health equity impact assessments, we would welcome further exploration of whether this has particular impacts for gender or age related trends.
- Regarding the role of electronic cigarettes in cessation of traditional tobacco smoking, we note that there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate. These are all important aspects of the work for public health, disease prevention and health promotion which our national and regional agencies carry out across Europe. As such, their evidence over time has clearly been reasonably taken into account in the Preliminary Opinion, which EuroHealthNet has drawn to their attention for consideration in national and local campaigns and interventions.

We hope the EU Institutions will also take it into account in deliberations concerning the EU TPD and related legislative and regulatory processes.

419	Champagne ac Maxime, P hodie, France	ABSTRACT	Revision needed on the abstract taking into account new and relevant contributions. https://www.sciencedirect.com/science/article/pii/S0376871620300181 https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787 https://www.sciencedirect.com/science/article/pii/S0304389420314060?via%3Dihub#sec0115	Please see table 1, answer 6.
420	Champagne ac Maxime, P hodie, France	ABSTRACT	lignes 46-47 "that flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation" Partially wrong, flavour has also an important contribution for smoking cessation. "that flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation, and smoking cessation" https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787	Please see table 1, answer 7.

421	Poirson Philippe, Sovape, France	ABSTRACT	<p>We welcome SCHEER's efforts to assess the topic of vaping in the context created by the TPD in the EU, prior to possible discussions on its revision. However this draft report fails to provide an adequate assessment in the European context on several points:</p> <p>1) It does not make a relative risk assessment between vaping and cigarettes when almost all vaping users in the EU are or have been smokers (McNeill, 2018 ; Farsalinos 2016);</p> <p>2) A large part of the studies cited concern products from outside the EU market; or, do not distinguish between uses with or without nicotine (or otherwise); and come from regulatory context radically different from that created by the TPD;</p> <p>3) Some important European studies are not reviewed;</p> <p>4) Another gap in relation to its mandate, the SCHEER draft never addresses the impact of regulations and/or actions of authorities on the issues addressed (Hua-Hie Yong, 2017 ; Ward, 2020).</p> <p>It would have been desirable the Scientific Committee analysed risks produced by the different national implementations: - evolution of smoking prevalence and evolution of the risks linked, between country tolerant to vaping, e.g. France, and country stigmatising vaping, e.g. Spain; - the effects of ban flavours and high taxes, e.g. Estonia, and the risks associated with the creation of a vast black market out of control.</p> <p>On the abstract text itself, we note: [p. 2 l. 14] The data presented in the report do not seem to allow asserting strong evidence of systemic cardiovascular effects (Benowitz, 2016 ; Shahab, 2017).</p> <p>[p.2 l.16] & [p.2 l.37] Data for products marketed under the TPD regime, which is the subject of this report, cannot support a carcinogenic risk by nitrosamine accumulation. Nicotine used in the EU is a highly purified grade (TPD art. 20 §3.d, 2014). This</p>	<p>Please see table 1, answer 1.</p> <p>Please see table 1, answer 8.</p> <p>Please see table 1, answer 2.</p> <p>This is out of the scope of the Opinion.</p> <p>The Opinion has been revised accordingly.</p> <p>Please see table 1, answer 4.</p>
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point indicates a more general confusion in the heterogeneous data used by the SCHEER, who does not seem to have discriminated the relevant data for specific European situation created by TPD.

[p. 2 l. 42 ss] The gateway hypothesis is not supported by the evidence presented in this report. The studies presented suffer from critical problems, including a lack of consideration of the risk co-factor of parental smoking and friends smoking, high attrition bias, etc. (Chan et al. 2020). The main meta-analysis presented has authors' self-report bias. The scientific criteria for validating a causal hypothesis as the gateway theory are not met (Etter, 2017). More robust European studies, notably the OFDT study in France, show effects incompatible with this hypothesis (Chyderiotis, 2019). All this chapter and conclusion need to be completely revised.

Please see table 1, answer 5.

[p. 2 l. 49 ss.] Many data were not included in the report. Cochrane review found 50 clinical studies and conclude to moderate-certainty evidence vaping with nicotine increase quit rate compared to NRT (Hartmann-Boyce, 2020). Preliminary results from other clinical studies (Eisenberg, ACC.20) are in the same direction. Santé Publique France has demonstrated that at least 700,000 people have quit smoking in a consolidated way thanks to vaping before 2017 (Pasquereau, 2017). Based on the Eurobarometer 429, an estimated 6 million EU citizens had quit with the help of vaping in 2014 (Farsalinos, 2016). The Smoking Toolkit Study showed that smoking cessation increased by ~70,000 net additional successful quitters thanks to vaping in 2017 in England (ASH, 2020). etc.

Please see table 1, answer 6.

We recommend a thorough and rigorous revision of the draft report before its transmission to the Commission.

[note: EC server blocked my upload files complement on studies references]

422 Muntadas-Prim
Angeles,A
NESVAP,
Spain

ABSTRACT
Page 2, lines 49-52
Comment
The SCHEER statement is simply not true. In fact, the evidence of the effectiveness of e-cigarettes in smoking cessation seems to be strong according to the latest Cochrane review: "More people probably stop smoking for at least six months using

Please see table 1, answer 6.

nicotine e-cigarettes than using nicotine replacement therapy (3 studies; 1498 people), or nicotine-free e cigarettes (3 studies; 802 people). We are uncertain if there is a difference between how many unwanted effects occur using nicotine e-cigarettes compared with using nicotine-free e-cigarettes, nicotine replacement therapy, no support or behavioural support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for all groups."

Ref:

Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theoudoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. (2020). Electronic Cigarettes for smoking cessation. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4

423	Gallus Silvano, Istituto di Ricerche Farmacologiche Mario Negri, Italy	ABSTRACT	<p>Abstract and main text: Along the text, please consider to substitute "second-hand exposure" with "exposure to second-hand aerosol from e-cigarette (SHA)". Moreover, substitute: "second-hand exposed persons" with "SHA exposed non-users" or "SHA exposed subjects".</p>	Thank you for this suggestion.
424	Pietsch Franz, Austrian Federal Ministry of Social, Health, Care and Consumer Protection, Austria	ABSTRACT	<p>Following SCHEER's invitation, the Austrian Federal Ministry of Health (MoH) sent the current report to relevant stakeholders with the request for comments. As far as feedback was given to the MoH, this feedback has been incorporated into the MoH's statement. In particular, the considerations and feedback from the Austrian MoH are based on the comments received from the addressed stakeholders (in particular of the Working Group "Addiction Prevention", the AGES and the Doctors' Initiative against Smoking Damage). The opinions expressed therein build the basis of the summarized positioning of the Austrian MoH. The MoH largely agrees with the conclusions in the three points made by SCHEER on</p> <ol style="list-style-type: none"> 1. "Risk assessment", 2. "Role in the initiation of smoking" and 3. "Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use". <p>The following points are of particular relevance to the MoH:</p> <p>ad. 1 "Risk assessment"</p> <ul style="list-style-type: none"> • E-cigarettes seem to cause less harm to the body than tobacco cigarettes. • E-cigarettes are also harmful to health, with particular evidence for the lungs and the cardiovascular system. 	Thank you for your support.

- Nicotine is suspected of being carcinogenic.
- Nicotine is addictive or maintains an addiction, regardless of whether this substance is consumed through tobacco cigarettes or e-cigarettes.
- The consumption of e-cigarettes and tobacco heaters is a more harmless form of consumption compared to conventional combusting cigarettes; However, there is a lack of scientific evidence for long-term harmlessness or harm reduction of e-cigarettes or tobacco heaters, as well as evidence for effective smoking cessation.

ad. 2 "Role in the initiation of smoking"

- The most common entry point into nicotine consumption is by far the tobacco cigarette, but the share of e-cigarettes is increasing.
- The most common previous form of e-cigarette use is tobacco use, but there are also non-smokers who start with e-cigarettes. The latest ESPAD results also show this development among young people.
- A gateway effect can be observed: Anyone who consumes e-cigarettes as the first nicotine product will start smoking tobacco cigarettes within the next few years - compared to those without e-cigarette experience - with a significantly higher probability.

ad. 3 "Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use"

- Switching from tobacco cigarettes to e-cigarettes is not a weaning process as it involves getting rid off nicotine.
- The e-cigarette can help some smokers to get rid off tobacco. As an aid in smoking cessation, however, it has no advantage over tested aids (e.g. nicotine substitutes).
- E-cigarettes usually are neither medical devices nor licid drugs or a regulated medical product with restricted access; that's why in a medical sense or medical goal setting it can not be seen as a contribution to a medicine based harm reduction.
- The reality and the most common form of consumption is "dual use", ie the combination of e-cigarettes and tobacco cigarettes.
- Switching from tobacco to e-cigarette use can prolong nicotine addiction, as users believe they are on the "safe side" in terms of health and no longer see any reason to pull off their habit.

The Austrian MoH sees the SCHEER report as a valuable and helpful interim assessment of the progressive e-cigarette consumption that has been relevant since almost 10 years, without taking into account any long-term effects or benefits.

In general the MoH agrees with the results of the SCHEER-report which

raises awareness and contributes to the development and implementation of strategies regarding legal based regulations on a national level taking into account all kinds of emerging tobacco products and its respective

425	Milton Anders,Snuskommisionen,Sweden	ABSTRACT	<p>Page 2 lines 7-40</p> <p>The SCHEER’s opinion has limited its assessment to comparing the health impacts of e-cigarettes versus abstaining from using any nicotine. However, most users of e-cigarettes are smokers and the assessment of the relative risk of using e-cigarettes should also be made compared to continued smoking. There is a large body of evidence reflecting that the relative risks of using e-cigarettes are less than continuing to smoke. As stated by public Health England in their report Evidence review of e-cigarettes and heated tobacco products 2018: “The health effects of cleaner nicotine products per se is important, but the key comparison should be with smoking as, to our knowledge, no-one in public health is recommending nicotine to never smokers”</p>	Please see table 1, answer 1.
			<p>Page 2 lines 43-44</p> <p>One of the conclusions of the SCHEER’s opinion is that “there is strong evidence that electronic cigarettes are a gateway to smoking for young people”. The term gateway implies that there is a causal relationship between the use of e-cigarettes and the transition to cigarette smoking and that the use of e-cigarettes will lead to smoking among people who would otherwise not have smoked. Most studies on the topic comes from the US. Circumstances in the US are not directly transferable to a EU context, as that the regulatory environment in the US is different from the countries where TPD2 has been implemented.</p>	Please see table 1, answer 5.
			<p>In the 2020 Public Health England evidence report on e-cigarettes Vaping in England 2020 the authors conclude that the evidence do not support that e-cigarettes are used extensively by youth who would otherwise not have smoked but rather find that the use is confined mostly to those who are smoking: “current vaping is mainly concentrated in young people who have experience of smoking. Less than 1% of 11- to 18-year-olds who have never smoked are current vapers” “the data presented here suggest that vaping has not undermined the declines in adult smoking” and To state a gateway effect, it is not just necessary to find a relationship between the use of e-cigarettes and the initiation of smoking but also to find a causation. Most of the studies included in the SHEER opinion do not provide evidence of a causative relationship. In 2020 the Swedish governmental agency Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) published a report based on a systematic review on e-cigarettes and smoking initiation the conclusions</p>	

were: “It is probable that experimentation with e-cigarettes may be a predictor for later initiation of cigarette smoking (certainty of evidence moderate). The certainty of evidence was higher among young individuals (certainty of evidence moderate) but could also be found among adults (certainty of evidence low). Association between experimentation with e-cigarettes and current use of cigarettes was also found (certainty of evidence moderate).”and “Based on the results of this systematic review, it is not possible to determine whether the associations found in the material are causal, or mainly statistical relationships. In most of the included studies, it is possible that confounders affect the outcome” The SBU report supports an association, but is not supportive of a gateway effect, even if it does not rule it out. The question on if there are a causative gateway effect or not should be subject to further research. The statement in the SHEER report “there is strong evidence that electronic cigarettes are a gateway to smoking for young people” should thus be moderated to “there is moderate-strong evidence that electronic cigarettes are associated with smoking for young people, but given the current evidence it is impossible to conclude if the relationship is causality.

426 No agreement to disclose personal data

ABSTRACT

Page 2 Line 7: THE OPINION FAILS TO CONSIDER THE RELATIVE RISK OF E-CIGARETTES COMPARED TO CONTINUED TOBACCO SMOKING:

The Opinion does not consider the potential health effects of e-cigarettes within a reduced risk context and relative to combustible cigarette smoking, thereby omitting the important role e-cigarette are playing in tobacco harm reduction amongst adult smokers who would otherwise continue to smoke. Instead, it focuses solely on the absolute risk of e-cigarettes which - although an important consideration for non-smokers’ use of vape products – fails to take into account that the overwhelming majority of users are former or current adult smokers who are specifically using e-cigarettes to reduce or cease cigarette consumption. In countries where governments and public health bodies have invested sufficient time in researching and debating the science, most have concluded e-cigarettes are significantly less harmful than cigarette smoking and can therefore contribute considerably to population-level tobacco harm reduction.

Although there is a need for more research into the long-term effects of e-cigarettes, the totality of the current scientific literature indicates any long-term risks are highly likely to be much lower compared to continued cigarette smoking[1]. Notably, estimations of the long-term public health impacts of e-cigarettes have indicated significant reductions in smoking-attributable deaths[2] even when conservative assumptions are made for relative health risks of e-cigarettes compared to combustible cigarettes and

For comparison with smoking: see Table 1, Answer 1.

for transitions between smoking, e-cigarettes and non-use[3]. We also respectively draw SCHEER's attention to the UK Government's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) recent and comprehensive report[4] which concluded: "In considering the comparison 'of [e-cigarettes] use with [combustible cigarette] smoking, the Committee concluded that the relative risk of adverse health effects would be expected to be substantially lower from [e-cigarettes]. This risk reduction would occur if people who are already smoking [combustible cigarettes] switch to [e-cigarettes], or if [e-cigarettes] are taken up instead of [combustible cigarettes]."

RELATIVE RISK MUST BE THE STARTING POINT FOR REGULATION AND SCIENTIFIC RESEARCH INTO E-CIGARETTES:

Any discussion on the role of e-cigarettes, together with scientific research methodology, must first take into consideration the potential risk and benefits compared to continued tobacco smoking. If this important starting point is discarded, then regulatory and policy frameworks will not reflect the tobacco harm reduction potential of e-cigarettes, and any associated public health gains will fail to materialise.

THE OPINION FAILS TO TAKE INTO CONSIDERATION THE POSITION OF NUMEROUS GOVERNMENTS, REGULATORS, PUBLIC HEALTH BODIES, AND TOBACCO CONTROL GROUPS THAT ENDORSE E-CIGARETTES:

Many global organizations have endorsed e-cigarettes as a tobacco harm reduction tool and advocate that adult smokers should transition to these products[5]. These include conclusions from Canada, UK, Germany, Denmark, New Zealand, France and other countries.

P2 L42: THE SCIENTIFIC AND REAL-WORLD EVIDENCE DOES NOT SUPPORT THE CONCLUSION THAT E-CIGARETTES ARE A GATEWAY TO SMOKING TOBACCO, BUT ONGOING MONITORING IS REQUIRED:

As referenced and discussed further down, there is limited credible scientific or real-world evidence that e-cigarettes are a gateway product to cigarette smoking for never-smoker youth or adults in countries where e-cigarettes are regulated and widely available to adult smokers.

This is outside the scope of the Opinion.

This is outside the scope of the Opinion.

Please see table 1, answer 5.



Abstract.pdf

427 Chaplia ABSTRACT
Maria,Con

Page2 lines 42 - 47: When it comes to vaping policies, it is important to keep in mind that vaping was invented as a safer

Please see table 1, answer 1.

	<p>sumer Choice Center,Uni ted States</p>		<p>alternative to conventional smoking, and therefore its main target audience are tobacco consumers. There are many variables that contribute to smoking rates among young people, and many recent studies that have concluded that vaping is a gateway to smoking have failed to take those into account. For example, one study found that adolescents who were less satisfied with their life, in general, were more likely to seek risky experiences and have a higher tendency to use illicit substances regularly. Lawmakers should therefore focus on solving issues such as illicit trade and mental health and ensure age restrictions are enforced.</p> <p>Page 2, Lines 49 - 52: Vaping has helped millions of smokers switch thereby lowering their health-associated risks. A study conducted by the University College London in 2019 analysed data from over 50,000 smokers from 2006 to 2017 and found that using e-cigarettes in order to quit was positively associated with the quit success rates, with every 1 per cent rise in use of e-cigs associated with a 0.06% increase in the quit success rate. The 2018 U.S. National Academies of Sciences, Engineering, and Medicine Report found that the smoking rate has decreased overall more rapidly since vaping became more prominent in the United States. Ref: Tan (2019). Individual, Family, and School Correlates across Patterns of High School Polysubstance Use Levy (2019). Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check Beard (2019). Association of prevalence of electronic cigarette use with smoking cessation and cigarette consumption in England: a time-series analysis between 2006 and 2017.</p>	<p>Please see table 1, answer 6.</p>
<p>428</p>	<p>Fernández Bueno Fernando,P lataforma para la Reducción del Daño por Tabaquismo, Spain</p>	<p>ABSTRACT</p>	<p>Page 2 lines 7-11 Comment The SCHEER's opinion seems to ignore a very important pillar when analyzing e-cigarettes: this products are intended to be a replacement of conventional cigarettes for those smokers that couldn't quit smoking. Therefore, any analysis of e-cigarettes effects should be compared with the product that they replace to (conventional cigarettes). SCHEER's opinion should reflect a comparison between electronic cigarettes and conventional cigarettes and not talk about absolute terms. The SCHEER's opinion focuses only on health impacts of e-cigs compared to non-</p>	<p>Please see table 1, answer 1.</p>

smoking. This approach would reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking. There is a large body of evidence demonstrating that electronic cigarettes are less harmful compared to continued smoking. For example, the Tobacco Advisory Group of the U.K.'s Royal College of Physicians, concluded the following in the report "Harm reduction in nicotine addiction: Helping people who can't quit", Oct. 2007,

"Since nicotine is the primary addictive constituent of tobacco smoke, the harm reduction approach for those who cannot otherwise quit smoking tobacco or who want to reduce the impact their smoking has on themselves and others is to substitute cigarettes with less hazardous alternatives. Even though smoking-related harms may be merely reduced rather than removed by this approach, many lives could also be saved and much morbidity prevented." Such conclusions should be reflected in the opinion.

It's worthy to analyze data from studies made in respiratory patients. The study made in COPD "Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up" was made in COPD patients. Complete data from this study were available from 44 COPD patients. Compared to baseline in the e-cig user group, there was a marked decline in the use of conventional cigarettes. Although there was no change in lung function, significant improvements in COPD exacerbation rates, CAT scores, and 6MWD were observed consistently in the EC user group over the 3-year period ($p \leq 0.01$). Similar findings were noted in COPD e-cigs users who also smoked conventional cigarettes ("dual users"). The study concludes that e-cig use may ameliorate objective and subjective COPD outcomes and that the benefits gained may persist long-term. EC use may reverse some of the harm resulting from tobacco smoking in COPD patients. A recent continuation of this study has demonstrated that these health improvements continue 5 years after start vaping.

References:

<https://cdn.shopify.com/s/files/1/0924/4392/files/harm-reduction-nicotineaddiction.pdf?15599436013786148553> A report by the Tobacco Advisory

Group of the Royal College of Physicians, Harm reduction in nicotine addiction Helping people who can't quit, October 2007

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6113943/>

Polosa R, Morjaria JB, Prosperini U, et al. Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. *Int J Chron Obstruct Pulmon Dis.* 2018; 13:2533-2542. Published 2018 Aug 22. doi:10.2147/COPD.S161138

https://journals.sagepub.com/doi/full/10.1177/2040622320961617?fbclid=IwAR2PQPpxtznyjb6IxISJx5rMP1Dencj1QIV-ohzJD_U8JVHhblCxQcyy3Vs&

Polosa R, Morjaria JB, Prosperini U, et al. COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Therapeutic Advances in Chronic Disease.* January 2020. doi:10.1177/2040622320961617

429	Fernández Bueno Fernando,P lataforma para la Reducción del Daño por Tabaquismo,Spain	ABSTRACT	<p>Page 2 lines 13-14</p> <p>The potential risk for cardiovascular disease from e-cigarette use has been mainly attributed to the effects of nicotine. Several studies have shown that nicotine intake does not elevate cardiovascular risk. A meta-analysis of 34 randomized controlled trials showed that NRTs did not pose any elevated risk for myocardial infarction, stroke, palpitations, angina, arrhythmia, or hypertension compared with placebo-treated patients. Long-term inhalation of nicotine was tested in mice in Waldhuhm et al 1996 and no adverse CV effects were observed. Use of NRTs in high-risk individuals was similarly not associated with an elevated risk for major adverse cardiovascular events (MACE). The greatest source of CV risk in tobacco is not nicotine but CO, not present in e-cigarettes. E cigarettes are a harm reduction tool FOR SMOKERS, not a harmless tool. Typically, similar concentrations of nicotine have been found in NRT users, many of whom have used these products for many years, even for a lifetime, without CV adverse effects.</p>	<p>Based on its assessment, the SCHEER concluded that the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is moderate.</p> <p>Please see table 1, answer 1.</p>
				
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430	Fernández Bueno Fernando,P lataforma para la Reducción del Daño por	ABSTRACT	<p>Page 2 lines 15-19</p> <p>Conclusions from Shahab et al 2017 found a 95% reduction of carcinogens in the body of ex-smoker vapers. The levels were similar to those of NRT users. This is an in vivo and real-life study. Stephens et al 2018 found that optimal combinations of device settings, liquid formulation and vaping behaviour normally result in e-cigarette emissions with much less carcinogenic potency than tobacco smoke.</p>	<p>Please see table 1, answer 1.</p>
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Tabaquismo,
Spain

References on comments to page 2, lines 15-19:

Stephens WE Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke

Tobacco Control 2018;27:10-17. <https://tobaccocontrol.bmj.com/content/27/1/10>
Maciej L. Goniewicz , Benjamin C. Blount , Jamie Brown et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users. Annals of Internal Medicine 2017;166:390-400. [Epub ahead of print 7 February 2017]. doi:<https://doi.org/10.7326/M16-1107>, <https://www.acpjournals.org/doi/10.7326/M16-1107>

431 Fernández Bueno Fernando,P
lataforma para la Reducción del Daño por Tabaquismo,
Spain

ABSTRACT

Page 2 lines 26-28
Product attractiveness (flavours) is absolutely essential for these devices to help smokers quit smoking. Adolescents should be protected through regulation, but adults should not be punished due to that.



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Please see table 1, answer 7.

432 Wyszynska-Szulc Agnieszka,
Philip Morris Products S.A.,
Switzerland

ABSTRACT

P. 2 l. 7-37
The SCHEER's conclusions on health impacts of e-cigarettes omit an important in our view aspect, i.e. the assessment of the relative risk of using e-cigarettes compared to smoking - and focus only on health impacts compared to non-smoking. This approach fails to reflect the reality of e-cigarettes use, i.e. the fact that these products are mainly used by smokers as alternatives to smoking. There is already a large body of evidence demonstrating that e-cigarettes are less harmful compared to continued smoking and we recommend to add such conclusion to the opinion, including the referenced here publications (U.K.'s Royal College of Physicians 2007; U.K.'s Royal College of Physicians 2016; McNeill 2015; COT 2020; DKFZ 2020).

Please see table 1, answer 1.

P. 2 l. 14
In our view there is no substantiation, included in the SCHEER's opinion, for describing here the weight of evidence as "strong". We therefore recommend not to use the word "strong" and instead reflect in the conclusions the large body of evidence showing that e-cigarettes are less harmful compared to continued smoking.

P. 2 1. 43-44
The SCHEER Opinion omits several important and recent studies from European countries that dismiss the gateway hypothesis and do not support SCHEER's conclusion that there is "strong" evidence that e-cigarettes are a gateway to smoking, including for young people. Therefore, we recommend to change the conclusions in the SCHEER's opinion in line with this evidence which we reference in our comments to section 6.6.

Please see table 1, answers 2 and 5.

P. 2 1. 47
Given that several studies show that most smokers use flavoured e-cigarettes to quit smoking, we suggest adding in the conclusion: "At the same time there is growing evidence that flavours may contribute to help smokers quit by switching to electronic cigarettes."

Please see table 1, answer 7.

P.2 1.49-52
There is growing evidence (Lucchiari 2020; Glasser 2020; Farsalinos 2020, Levy 2020, Hartmann-Boyce 2020) which demonstrates the effectiveness of nicotine containing e-cigarettes in smoking cessation and smoking reduction. Therefore, we believe there is no substantiation to the conclusion that there is "weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate." We suggest to change the conclusion to be consistent with the most recent evidence.

Please see table 1, answer 6.

433 Fernández Bueno, P
ABSTRACT
Fernando, P
lataforma para la Reducción del Daño por Tabaquismo, Spain

Page 2 lines 30-37
There is no evidence that the concentration of substances in the exhaled vapor released into the environment has the slightest ability to cause clinical effects on bystanders. SCHEER should compare these concentrations and composition with the air quality in any standard city (containing the solid particulate matter from the engines of millions of cars daily).

Please see table 1, answer 4.



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434	Fernández Bueno, Fernando, Plataforma para la Reducción del Daño por Tabaquismo, Spain	ABSTRACT	Page 2 lines 42-47	In regards the “gateway effect” of the e-cig the SCHEER’s opinion concludes that “there is strong evidence that electronic cigarettes are a gateway to smoking for young people”. This evidence is primarily coming from the U.S. and not EU. SCHEER should also consider the “common liability bias” and the young people smoking rates evolution in the US data.	Please see table 1, answer 5.
			Later in the opinion it is stated, among other things, that: the electronic cigarettes available in Europe differ frequently from those available in the U.S. (e.g. including with regard to regulatory requirements - much higher nicotine concentrations in U.S. than allowed by the EU Tobacco Products Directive as well as other requirements of the EU legislation, which is more stringent than in U.S.). The available evidence from the EU countries does not support the conclusion that there is a strong evidence that electronic cigarettes are a gateway to smoking. Some EU countries have generated strong evidences in that direction, as UK. As an example, the study of Bauld et al “Young People’s Use of E-Cigarettes across the United Kingdom: Findings from Five Surveys 2015–2017” summarizes that surveys across the UK show a consistent pattern: most e-cigarette experimentation does not turn into regular use, and levels of regular use in young people who have never smoked remain very low. Therefore, the evidence for the EU is weak in this regard.	Please see table 1, answer 8.	
			The SCHEER’s opinion has ignored the evidences that support that the gate-away effect, (entrance- door effect) of the e-cig is weak, based on some studies from different European countries:		
			The importance of flavors is discussed in the article of Romijnders; The article reflects that “. . . the importance and complexity of regulating e-liquid flavors in a way that both the decision to switch towards vaping (for smokers) and the decision to refrain from vaping (for never-users) are supported. Ideally, regulation should allow marketing of e-liquid flavors that stimulate smokers and dual users to keep or start using e-cigarettes. To make never-users more negative about and keep them from using e-cigarettes, product appeal should be reduced by, for example, restricting the marketing	Please see table 1, answer 7.	

and promotion of e-liquid flavors that they find particularly appealing.” These conclusions should be reflected in the final opinion of the SCHEER. Additionally, the same publication demonstrates that among participants who reported to never have smoked and never have used an e-cigarette the majority (68%) of the participants were not interested in trying a flavored e-cigarette.

In France, data from Chyderiotis (2020) show that adolescents who have tried electronic cigarettes are less likely to later transition to daily smoking than those who have not. According to ASH UK youth mainly vape to give it a try (52.4%) not because they think it looks cool (1.0%). According to data from Italy (Gorini 2020), that electronic cigarettes do not seem to have determined an increase in tobacco smoking between 2010 and 2018. According to the latest 2020 report by the German Cancer Research Center (DKFZ), there is little evidence for a gateway effect on a population level. All these evidences should be reflected in the SCHEER’s opinion

Please see table 1, answer 6.



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<p>435 O'Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy</p>	<p>ABSTRACT</p>	<p>P2L2 The statement on cardiovascular risk is contradicted by the National Academies of Sciences, Engineering, and Medicine systematic review (2018) that states “Conclusion 9-1. There is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification)” (p.7 emphasis in original). There are no empirical data on cardiovascular events in ENDS users (Benowitz and Fraiman, 2019). Furthermore, the WHO Study Group on Tobacco Product Regulation (2019) states that the evidence on cardiovascular risk is controversial, and risk may be attributed solely to nicotine. The Abstract should state that the evidence on cardiovascular risks is inconclusive and risks can be attributed to nicotine.</p>	<p>The opinion has been revised accordingly.</p>
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P2L42-44 Two large population surveys, one from France, demonstrate a null effect of electronic cigarette initiation or ever-use on an increased uptake of regular cigarette smoking by youth, and in fact showed a decrease in the prevalence of regular cigarette use. Other studies propose a common liabilities hypothesis. The Abstract should state that evidence is mixed on a gateway effect.

Please see table 1, answer 5.

P2L45 The Abstract should add a substantial number of youth and adults use non-nicotine liquids.

P2L46-47 The Abstract should add curiosity is the primary reason for youth experimentation.

P2L50 The Abstract should classify the cessation evidence as moderate in accord with the current Cochrane review (Hartmann-Boyce et al. 2020).

436 Fernández Bueno Fernando, Plataforma para la Reducción del Daño por Tabaquismo, Spain

ABSTRACT Page 2 lines 49-52
 There is strong evidence that e-cigarettes are a powerful tool to help people quit smoking, even more effectively than the usual NRT therapies. SCHEER should examine the recent Cochrane review, but there are many more data and studies to value. SCHEER should also analyse how misinformation about electronic cigarettes could influence in the rate of quit attempts. Misinformation and misperceptions is the main cause of smokers not converting to vaping and continue smoking.

Please see table 1, answer 6.



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437 Serafimov Lubomir, Bulgarian Vape Association of Manufacturers,

ABSTRACT Page 2 lines 7-40
 We would like to express our main concerns with the SCHEER preliminary Opinion and they refer to two major points:
 The Opinion does not provide useful scientific information for policymakers; rather it provides selective and often misleading judgements on the used literature.

		<p>The Opinion also omits the most important aspect of the assessment of the health impact of electronic cigarettes –namely, the assessment of the relative risk of using electronic cigarettes compared to smoking and focuses only on health impacts compared to non-smoking. This approach is very selective and generally does not reflect the reality of the usage of electronic cigarettes, i.e. the fact that they are primarily used as alternatives to smoking. There is a numerous papers and scientific reports evidencing that electronic cigarettes are less harmful compared to conventional tobacco cigarettes.</p>	<p>Please see table 1, answer 1.</p>
<p>438 Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E-liquid,Bulgaria</p>	<p>France Vapotage France Vapotage ,FRANCE VAPOTAGE ,France</p>	<p>ABSTRACT</p> <p>France Vapotage is the federation of vaping products manufacturers operating in France. France Vapotage is very disappointed by the SCHEER preliminary opinion which fails to address the potential benefits associated with e-cigarettes as an alternative to smoking thus ignoring the public health principle of tobacco harm reduction. It states that e-cigarettes have negative impacts on health without positioning these harms in comparison to cigarettes. It does not take into account a growing body of international, independent scientific evidence showing that exclusive e-cigarette use reduces users’ exposure to toxicants and remains an effective component of tobacco harm reduction helping smokers to quit . SCHEER’s Rules of Procedure requirements include transparency and consideration of the best scientific evidence but the selective evidence does not meet these standards.</p> <p>Regarding Cardiovascular risks: The claim “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” (LN13-14) is inconsistent with available evidence. SCHEER could review the above statement so that it reflects current scientific evidence</p> <ul style="list-style-type: none"> - Available evidence supporting cardiovascular improvements for adults switching to e-cigarettes (relative risks) is strong, and that there no increased cardiovascular risk of nicotine exposure in consumers who have no underlying cardiovascular pathology. - The conclusions made by SCHEER are based on reviewing 	<p>Please see table 1, answer 1.</p> <p>Please see table 1, answer 6. The role of electronic cigarettes in quit smoking is addressed in chapter 6.7 in the Opinion.</p> <p>The Opinion has been revised accordingly.</p>

limited and older studies, mistakenly inferring short-term, transient effects with longer-term outcomes supported by misleadingly and unscientifically assuming e-cigarette effects are comparable with those of cigarettes.

- A significant amount of scientific literature on the cardiovascular effects of e-cigarettes has been omitted.

Regarding e-cigarettes and young people/"gateway" effect
The claim "there is strong evidence that electronic cigarettes are a gateway to smoking for young people" (LN42-44) is inconsistent with evidence presented in available studies. This statement could be reviewed to show a larger review of available literature

- It has been concluded by a number of experts that these studies do not provide evidence that allows us to conclude in a direct association between e-cigarette use and subsequent cigarette smoking, nor do they define how to test the gateway theory.
- The 'gateway' arguments have been criticized by many comprehensive reviews and studies, that have concluded that no reliable evidence exists of a gateway effect.

Please see table 1, answer 5.

Regarding e-cigarettes effectiveness in helping smokers to quit
The claim "there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit" (LN50-52) is inconsistent with scientific evidence. We believe that the evidence should not be considered as "weak" and that this claim should be reconsidered based on available scientific literature

- While e-cigarettes are not medicinal smoking cessation devices, the opinion does not consider a number of studies that show that millions of EU and other smokers have managed to successfully switch to e-cigarettes.
- In particular, the effect and safety of e-cigarette to help smokers achieve long-term abstinence has been evaluated by the 2020 Cochrane review.

Please see table 1, answer 6.

France Vapotage hopes SCHEER will review its report and conclusions. As the report omits latest scientific evidence, does a selective and non-transparent analysis, we believe that it does not comply with the SCHEER own standards and the Opinions terms of reference We strongly believe that regulation should be based on

439

Pietsch Franz, Austrian Federal Ministry of Social, Health, Care and Consumer Protection, Austria

ABSTRACT

an objective analysis of evidence as well as the principles of tobacco harm reduction.

Following SCHEER's invitation, the Austrian Federal Ministry of Health (MoH) sent the current report to relevant stakeholders with the request for comments. As far as feedback was given to the MoH, this feedback has been incorporated into the MoH's statement.

In particular, the considerations and feedback from the Austrian MoH are based on the comments received from the addressed stakeholders (in particular of the Working Group "Addiction Prevention", the AGES and the Doctors' Initiative against Smoking Damage). The opinions expressed therein build the basis of the summarized positioning of the Austrian MoH. The MoH largely agrees with the conclusions in the three points made by SCHEER

1. "Risk assessment",
2. "Role in the initiation of smoking" and
3. "Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use".

The following points are of particular relevance to the MoH:

- ad. 1 "Risk assessment"
- E-cigarettes seem to cause less harm to the body than tobacco cigarettes.
 - E-cigarettes are also harmful to health, with particular evidence for the lungs and the cardiovascular system.
 - Nicotine is suspected of being carcinogenic.
 - Nicotine is addictive or maintains an addiction, regardless of whether this substance is consumed through tobacco cigarettes or e-cigarettes.
 - The consumption of e-cigarettes and tobacco heaters is a more harmless form of consumption compared to conventional combusting cigarettes; However, there is a lack of scientific evidence for long-term harmlessness or harm reduction of e-cigarettes or tobacco heaters, as well as evidence for effective smoking cessation.

ad. 2 "Role in the initiation of smoking"

- The most common entry point into nicotine consumption is by far the tobacco cigarette, but the share of e-cigarettes is increasing.
- The most common previous form of e-cigarette use is tobacco use, but there are also non-smokers who start with e-cigarettes. The latest ESPAD results also show this development among young people.
- A gateway effect can be observed: Anyone who consumes e-cigarettes as the first nicotine product will start smoking tobacco cigarettes within the next few years - compared to those without e-cigarette experience - with a

Thank you for your support.

erroneous conclusions will disproportionately influence readers of this report.

441 Olteanu
Vlad, JUU
L Labs
Inc., Belgium

ABSTRACT
Initially, there are several inconsistencies between conclusions in the abstract and the conclusions in the more in-depth analysis in the body of the report. The impact of this cannot be overstated given the importance of an abstract -it is the part of a scientific report that is most visible. A 1987 editorial by the editors of Obstetrics and Gynaecology noted that what the reader “deserves to be told is some indication of the report's purpose, methodology, and implications.” The SCHEER abstract does not do this. An example of an inconsistency is where the abstract states that “the overall weight of evidence for risks of local irritative damage to the respiratory tract is i) moderate for heavy users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine, and ii) not to be excluded for average and light users. However, the overall reported incidence is low.” (pg 2, ln 9; emphasis added). This conclusion is at odds, however, with the text of the health effects section of the report which states that “If assessed, acute mouth / throat irritation, and cough are reported by a sub-group of users (Polosa et al., 2011; Palamidas et al., 2017) and that these effects are not attributed to the nicotine content (Palamidas et al., 2017). These effects are in fact thought to be caused by hyperventilation, which is associated with long puffing time (Morjaria et al., 2011).” (pg 47, ln 13; emphasis added) More egregious is the discrepancy between the conclusion in the abstract that “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong,” (pg 2, ln 13) and the statement within the text of health effects section, where it actually says the European Heart Network (EHN) concluded that ...’the long-term effects on the cardiovascular system are still unknown due to the lack of relevant data” (pg 47, ln 28-36). Inconsistencies between the abstract and in-depth analysis coupled with the fact that most readers will only read the abstract, and not the longer report, increase the chances that inconsistent conclusions will be amplified by individual readers and media but, perhaps also by policymakers tasked with reconciling this scientific opinion with public health interests. Scientific abstracts disproportionately influence media press releases and coverage.

The SCHEER revised carefully the Summary and the Abstract in the final Opinion.

Regarding cardiovascular effects, the Opinion has been revised accordingly.

An abstract should act as an introduction and review of the entire document. If intended to act as a standalone entity, it should include information regarding the background, purpose, results, and contents of the work. This abstract does not include any of these necessary details, but instead presents a list of conclusions without any context. This is at odds with other public health agency reports that do not provide an abstract but focus on a more detailed summary of each section at the front of the report. We recommend that the committee focuses the abstract on the report's purpose, methodology, and implications and reserves discussion of the conclusions to a longer summary similar to previous comprehensive reports such as PHE and NASEM

Ref:

Yavchitz et al (2012). Misrepresentation of Randomized Controlled Trials in Press Releases and News Coverage: A Cohort Study. PLoS Medicine. September 2012 | Volume 9 | Issue 9 | e1001308

McNeill et al (2018). Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England. Public Health England, 2018.

NASEM (2018). National Academies of Sciences, Engineering and Medicine Public health consequences of ecigarettes. Washington DC: The National Academies Press; 2018.

442 Arffman ABSTRACT
Päivi,Vape
rs
Finland,Fi
nland

ABSTRACT: "The overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong."

(Page 2, lines 13-14)

See also:

— SCIENTIFIC OPINION: Overall assessment for electronic cigarette. (Page 15, lines 5-17).

— RATIONALE: 6.5.4 Human evidence for health impacts of electronic cigarettes/Cardiovascular diseases (page 47, line 27 - page 48, line 47)

— RATIONALE: 6.5.5.6 Conclusions/Cardiovascular diseases (page 61, lines 15-27)

Most e-cigarette users are smokers/ex-smokers, so they already have a higher than average risk of heart problems. An association observed in some studies between the use of e-cigarettes and the increased risk of heart disease is therefore more likely to be explained by past, possibly very long-lasting smoking, than with the current use of e-cigarettes.

The Opinion has been revised accordingly.

Please see table 1, answer 1.

For example, the Bhatta & Glantz -study (2019) found an association between the use of e-cigarettes and increased risk of heart attack, but the association disappeared when those users who had had a heart attack before starting to use e-cigarettes were excluded from the analysis (the study has since been retracted).

The potential heart risks of e-cigarettes are primarily associated with nicotine. The cardiac effects of nicotine are however mild and transient, and no problems have been observed with long-term use of, for example, pharmaceutical nicotine replacement products. In a systematic review published in 2018 (Rostron et al.), Swedish-type snus was not found to increase the risk of cardiovascular disease.

The heart risks of smoking are mainly caused by harmful substances generated during combustion. There is no combustion in e-cigarettes, so switching from smoking to e-cigarette use results in significant benefit to heart health (Benowitz et al., 2016).

A study published in 2019 (George et al.) found a significant improvement in heart health as early as one month after switching from smoking to e-cigarette use. Another recent study found that switching from smoking to e-cigarette use reduced arterial stiffness and oxidative stress after four months of use (Ikonomidis et al., 2020).

Ref:

Rodu (2020). A re-analysis of e-cigarette use and heart attacks in PATH wave 1 data
Rostron (2018). Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis.

Benowitz (no year). Cardiovascular Toxicity of Nicotine: Implications for Electronic Cigarette Use

George (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes

Ikonomidis (2020). Effects of electronic cigarette on platelet and vascular function after four months of use

443 Thielen ABSTRACT
Anja,BVT
E
Bundesver

The preliminary SCHEER opinion does not fulfil the mandate to support the Commission in assessing the potential need for legislative amendments within the TPD framework.

band der
Tabakwirts-
chaft und
neuartiger
Erzeugnisse,
Germany

Switching to e-cigarettes can be a much less harmful alternative for adult smokers. Therefore, the assessment should place the health risk of e-cigarettes in the appropriate context. The principle of Tobacco Harm Reduction should be acknowledged when evaluating e-cigarettes in order to give adult smokers the opportunity to consume potentially less harmful nicotine products. We respectfully request SCHEER to review its conclusions.

Please see table 1, answer 1.

LN 13-14 "Risks to the cardiovascular system"
While e-cigarettes are not safe, the scientific research indicates a rapid improvement of vascular function when switching from combustible cigarettes to e-cigarettes and therefore suggests that from a vascular perspective, e-cigarettes may be a less harmful alternative to combustible cigarettes. [1] Acute effects of delivering nicotine on vascular function cannot be used as a prognostic marker for cardiovascular risk. [2]

LN 15-16 "Risks for carcinogenicity of the respiratory tract"
While there is substantial evidence that some chemicals present in e-cigarette aerosols (e.g. formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis in in-vitro experiments, it remains to be determined whether the level of exposure is high enough to contribute to human carcinogenesis. The available data from emissions of e-cigarettes should also be compared with data from emissions of tobacco cigarettes. An assessment in this context would show that the exposure to harmful substances is considerably lower for consumers of e-cigarettes compared to tobacco smoke.

LN 42-44 "Electronic cigarettes are an initiation to smoking for young people"
SCHEER concludes in its preliminary opinion that there is strong evidence for this thesis, however the claim is inconsistent by the evidence presented. These studies fail to support the direct association between e-cigarette use and resulting cigarette smoking or even define how the gateway theory can be tested. [3]

Please see table 1, answer 5.

In Germany, the consumption of e-cigarettes and tobacco products is routinely monitored. The proportion of young people (14-17 year-olds) who use e-cigarettes regularly is 2.1% (2019) and has

not increased since 2016. [4] In contrast, the proportion of young people who smoke is declining sharply: while 27.5 percent of young people were smokers in 2001, this figure was only 6.6 percent in 2018. [5] This trend is unbroken, despite the introduction of the e-cigarette.

LN 50-52 "Effectiveness of electronic cigarettes in smoke cessation"

SCHEER has concluded that the weight of evidence is weak; the conclusion is inconsistent with the scientific evidence. [6] According to independent organizations, millions of smokers, globally and in the EU, have successfully switched to e-cigarettes.

Over 60% of the German population estimates the health risks of an e-cigarette to be higher or as high as the risks of a tobacco cigarette. Only six per cent of the Germans assume that e-cigarettes are clearly less harmful than tobacco cigarettes. [7] By this estimate the chances of the e-cigarette for smoking cessation are massively underestimated. SCHEER continues to consolidate this attitude.

In Germany, scientists have clearly positioned themselves to the fact that the population and especially smokers should be informed in a differentiated way about the advantages of e-cigarettes: e-cigarettes are not harmless, but a less harmful alternative to smoking. [8]



ref-443.docx

Please see table 1, answer 6.

444 Arffman ABSTRACT
Päivi, Vapers
Finland, Finland

”The overall weight of evidence for risks of carcinogenicity of the respiratory tract due to long-term, cumulative exposure to nitrosamines and due to exposure to acetaldehyde and formaldehyde is weak to moderate.” (Page 2, lines 15-17)

See also:
— SCIENTIFIC OPINION: Evidence for risk for carcinogenicity of the respiratory tract due to long-term, cumulative exposure to nitrosamines and due to exposure to acetaldehyde and formaldehyde

Thank you for your comment.

page 15, lines 19-34
 — RATIONALE: The overall weight of evidence for risk of respiratory tract carcinogenicity due to long-term, cumulative exposure to nitrosamines and due to exposure to acetaldehyde and formaldehyde (page 61, line 29 - page 62, line 5
 Studies to date have estimated the risk of cancer from the use of e-cigarettes to be very low. For example, a study by Stephens (2017) estimates that the risk of cancer is generally <1% of the risks of smoking and a Public Health England review (2018) estimates the cancer risk to be largely less than 0.4%. A Kosmider et al. study (2020) on acetaldehyde and formaldehyde exposure from e-cigarettes found the cancer risk to be 3117-21818 times smaller compared to smoking. A study by Cancer Research UK (2017) found long-term users of e-cigarettes to have levels of carcinogens and toxicants comparable to users of pharmaceutical nicotine replacement products.

Ref:

Stephens (2017). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke
 Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England, pages 155-157

Kosmider (2020). Daily exposure to formaldehyde and acetaldehyde and potential health risk associated with use of high and low nicotine e-liquid concentrations

Shahab (2017). Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users A Cross-sectional Study

445 Arffman ABSTRACT
 Päivi, Vapers
 Finland, Finland

”SCHEER concludes that there is strong evidence that electronic cigarettes are a gateway to smoking for young people.” (Page 2, lines 43-44)

See also:

—SCIENTIFIC OPINION: Role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people

(page 16, line 27 - page 18, line 39)

— RATIONALE: Health effects of electronic cigarette use on young populations, children and adolescents (page 52, lines 13-49)

— RATIONALE: Role as a gateway product or renormalisation of traditional tobacco smoking

(page 67, lines 11-24)

— RATIONALE: Experimentation with tobacco products among

non-tobacco using youth that experiment with electronic cigarettes (gateway) (page 67, line 26 - page 68, line 8)
 — RATIONALE: Experimentation with electronic cigarettes among non-smoking adults and youth in the EU (page 69, line 10 - page 70, line 15)
 E-cigarettes have not acted as a gateway to smoking, but if a gate is to be seen, it is away from smoking. Smoking has not increased, but has decreased faster than before alongside the increase in the use of e-cigarettes. One obvious reason for this is that most users of e-cigarettes are smokers or ex-smokers. Instead, regular use of e-cigarettes among never-smokers has remained very low (<1%).

Ref:

Levy (2019). Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check

In 2019 around half as many Britons now vape as smoke, and the majority are ex-smoker. ASH Press release.

Glasser (2020). Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey

ASH (2019). Use of e-cigarettes among young people in Great Britain

Zhu (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys

Please see table 1, answer 1.

446 Arffman ABSTRACT
 Päivi, Vapers
 Finland, Finland

”There is also strong evidence that [...] flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation.” (Page 2, lines 44-47).

See also:

— SCIENTIFIC OPINION: Role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people (page 17, line 34 - page 18, line 39)

— RATIONALE: Role in the initiation of smoking (particularly focusing on young people/Flavours (page 64, line 34 - page 66, line 2)

Flavours are an essential part of the use of e-cigarettes, without which e-liquids would be in practice tasteless. A range of flavours corresponding to different taste preferences is also needed because e-cigarettes cannot realistically mimic the taste of smoking cigarettes.

Smokers who have quit or are trying to quit smoking find flavours to be important when replacing cigarettes with e-cigarettes. According to a survey in 2018 (Farsalinos et al.), comprising of

Please see table 1, answer 7.

about 70,000 adult users of e-cigarettes, the majority of adult users, about 90%, use flavours like fruit, confectionery, dessert, etc. So these flavours are by no means particularly favored by youth. Flavours are not the main reason for young people's e-cigarette experiments, but curiosity and the same risk predisposing factors than in young people experimenting with tobacco. Because of this, young people who try e-cigarettes are largely the same young people who are potentially likely to try smoking cigarettes.

Ref:

Farsalinos et al. (not published). Patterns of flavored e-cigarette use among adults vapers in the United States: an internet survey.

Russell et al 2018: Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA

Kim (2020). The Relationship Between Electronic Cigarette Use and Conventional Cigarette Smoking Is Largely Attributable to Shared Risk Factors

Kinouani (2019). Motivations for using electronic cigarettes in young adults: A systematic review

447	Arffman Päivi, Vapers Finland, Finland	ABSTRACT	<p>”SCHEER concludes that there is weak evidence for the support of electronic cigarettes effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate.” (Page 2, lines 50-52).</p> <p>See also: — SCIENTIFIC OPINION: 3. Role of electronic cigarettes in cessation of traditional tobacco smoking (page 18, line 41 - page 19, line 7) — RATIONALE: 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use (page 70, line 18 - page 71, line 34)</p> <p>Multiple studies have shown the use of e-cigarettes to increase the probability of quitting smoking. E-cigarettes have also been proven to be more effective than nicotine replacement products for this purpose. These facts are stated e.g. in a recent Cochrane systematic review of 50 studies.</p> <p>Hartmann-Boyce (2020) Electronic cigarettes for smoking cessation (Review).</p>	Please see table 1, answer 6.
448	Arffman Päivi, Vapers	ABSTRACT	<p>”The overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong.” (Page 2, lines 13-</p>	The Opinion has been revised accordingly.

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Finland,Fi
nland

14).

See also:

— SCIENTIFIC OPINION: Overall assessment for electronic cigarette

(page 15, lines 5-17)

— RATIONALE: 6.5.4 Human evidence for health impacts of electronic cigarettes/Cardiovascular diseases (page 47, line 27 - page 48, line 47)

— RATIONALE: 6.5.5.6 Conclusions/Cardiovascular diseases (page 61, lines 15-27)

Most e-cigarette users are smokers/ex-smokers, so they already have a higher than average risk of heart problems. An association observed in some studies between the use of e-cigarettes and the increased risk of heart disease is therefore more likely to be explained by past, possibly very long-lasting smoking, than with the current use of e-cigarettes.

For example, the Bhatta & Glantz -study (2019) found an association between the use of e-cigarettes and increased risk of heart attack, but the association disappeared when those users who had had a heart attack before starting to use e-cigarettes were excluded from the analysis (the study has since been retracted). The potential heart risks of e-cigarettes are primarily associated with nicotine. The cardiac effects of nicotine are however mild and transient, and no problems have been observed with long-term use of, for example, pharmaceutical nicotine replacement products. In a systematic review published in 2018 (Rostron et al.), Swedish-type snus was not found to increase the risk of cardiovascular disease.

The heart risks of smoking are mainly caused by harmful substances generated during combustion. There is no combustion in e-cigarettes, so switching from smoking to e-cigarette use results in significant benefit to heart health (Benowitz et al., 2016). A study published in 2019 (George et al.) found a significant improvement in heart health as early as one month after switching from smoking to e-cigarette use. Another recent study found that switching from smoking to e-cigarette use reduced arterial stiffness and oxidative stress after four months of use (Ikonomidis et al., 2020).

Ref:
 Rodu (2020). A re-analysis of e-cigarette use and heart attacks in PATH wave 1 data
 Rostron (2018). Smokeless tobacco use and circulatory disease risk: a systematic review and meta-analysis.
 Benowitz (no year). Cardiovascular Toxicity of Nicotine: Implications for Electronic Cigarette Use
 George (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes
 Ikonomidis (2020). Effects of electronic cigarette on platelet and vascular function after four months of use

449	Bamberger Claude,Aiduce,France	ABSTRACT	<p>The abstract seems to be only available in English, as well as the report, as well as the consultation. This make the document and the consultation unavailable for a large part of the population. As a consumer association, and citizen, we regret it but will participate in English for our members and the French & French speaking Belgian vapers. La synthèse semble disponible uniquement en Anglais, tout comme le rapport, tout comme la consultation. Cela rend le document et la consultation inaccessible pour une large proportion de la population. En tant qu'association de consommateurs, et citoyens, nous le regrettons mais participerons en Anglais pour nos adhérents, les vapoteurs Français et Belges Francophones.</p>	Thank you for your comment.
450	Accorinti Sandro,-- ,Italy	ABSTRACT	<p>Page 2 lines 13-14 “The overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” Comment: Nicotine produces minor cardiovascular events but not major ones. CV risk in smoking comes from CO, not nicotine. "Snus delivers a high dose of nicotine with possible hemodynamic effects, but its impact on cardiovascular morbidity and mortality is uncertain." And "toxic components other than nicotine appear implicated in the pathophysiology of smoking related ischemic heart disease." Nicotine concentrations in NRT users’ plasma comparable to those using e-cigarettes, and: “The use of NRT is not associated with any increase in the risk of myocardial infarction, stroke, or death.” “While people with established CVD might incur some increased risk from e-cigarette use, the risk is certainly much less than that of smoking. If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be</p>	The Opinion has been revised accordingly.

substantially reduced and there would likely be a substantial net benefit for cardiovascular health.”

451	Accorinti Sandro,-- ,Italy	ABSTRACT	<p>ABSTRACT</p> <p>Page 2 lines 42-44</p> <p>Regarding the role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people, the SCHEER concludes that there is strong evidence that electronic cigarettes are a gateway</p> <p>Comment:</p> <p>SCHEER cites papers showing smoking and vaping association & interprets the link as causal. “Gateway” is impossible to determine: “We strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field.” “If a true gateway effect were to exist, it would probably have little effect on smoking prevalence. No available evidence exists that increasing e-cigarette use has slowed the decline in smoking prevalence; indeed, the decline appears to have accelerated.” Lee “There is a longitudinal association between adolescent vaping and smoking initiation; however, the evidence is limited by publication bias, high sample attrition and inadequate adjustment for potential confounders.”</p>	Please see table 1, answer 5.
452	Michel Nicolas,As sociation Romande des Profession nels de la Vape,Swit zerland	ABSTRACT	<p>ABSTRACT</p> <p>Page 2, line 7 to 37</p> <p>As a general rule, the SCHEER report is limited to saying what is the state of science concerning the various elements, ie whether we know enough to make a decision or not. However, this report does not say what the scientific conclusions are, whether they are strong or weak. Especially when the evidence is considered strong, it means that toxicity should be able to be estimated. For existing studies,</p> <ul style="list-style-type: none"> • Are the quantities of toxic emissions higher or lower than the standards? In particular regarding passive vaping, very few studies indicate that the standards can, under extreme conditions, be exceeded. • Compared to the toxicity of a cigarette, (or any other object emitting the same type of toxicity, such as candles concerning aldehydes) are the quantities of toxic emissions detected in the studies higher, lower or equivalent? • Is there clinical cases to support the claims of toxicity? 	Please see Table 1, answer 1. The SCHEER has quantified the risks according to their Guidance on the weight of evidence.

Although, as with any new product, we do not yet have 50 years of hindsight but after more than 10 years of existence and on a current estimated panel of several tens of millions of users, the absence or presence of clinical cases is already a clue. For example, studies exist on the weight of new-borns or premature births when the mother smokes or vapes. The term being 9 months, a follow-up of 10 years is already sufficient to rule on this subject. The evolution of COPD or the frequency of asthma attacks in smokers passing to vape are also short or medium term indicators that we have. By not quantifying the degree of emission of toxic compounds, by not giving a scale of magnitude, this report will lead the EU commission to make the wrong decision on the basis of concealing evidence.

To cite just one example per point given, here are some references that might appear in your report in order to quantify toxicity: «Although the e-cig vapours did not induce sufficient cell mortality to calculate an ED50 (whatever the tested e-cig power or model), ED50 was 45 puffs for HTP aerosol and 2 puffs for 3R4F cigarette smoke.»

<https://www.sciencedirect.com/science/article/pii/S0304389420314060>

«Concentrations of vaping-related chemicals in our air samples were below occupational exposure limits.»

<https://www.cdc.gov/niosh/hhe/reports/pdfs/2015-0107-3279.pdf>

«The birthweight of infants born to EC users is similar to that of non-smokers, and significantly greater than cigarette smokers. Dual users of both cigarettes and EC have a birthweight similar to that of smokers»

<https://obgyn.onlinelibrary.wiley.com/doi/abs/10.1111/1471-0528.16110>

When it comes to talking about the nicotine level, page 66, no worries about comparing vape and tobacco. Without mention, however, that a dose equivalent to a cigarette means interesting efficacy as a substitute product or as a smoking cessation tool. On the other hand, when it comes to toxicity, no comparison is made with cigarettes.

453	No agreement to disclose	ABSTRACT	Page 2	lines 7-40	While it is clear that electronic cigarettes pose a degree of risk, the abstract fails taking into consideration the role these products have Please see table 1, answer 1.
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	personal data	<p>with regards to the concept of reducing smoking related harm.</p> <p>It has been well documented over the years that traditional smoking cessation methods have come short of delivering desired outcomes – significantly reducing the number of smokers. Official data from the Czech Republic confirm this trend. (The National Institute of Public Health, http://www.szu.cz/uploads/documents/szu/aktual/zprava_tabak_al_kohol_cr_2019.pdf)</p> <p>Therefore, the report should not appropriate electronic cigarettes with non-smoking but with the use of combustible tobacco products producing tar and causing serious smoking related diseases.</p> <p>On behalf of KELK we strongly recommend the European Commission to reflect upon the relative risk associated with individual product categories as one of primary assumptions.</p>	Please see table 1, answers 5 and 6.
454	Bamberger Claude,Aid uce, France	<p>ABSTRACT</p> <p>(cf. other comments for the detail on each concerned chapter) L13, you state "the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong" based on 12 references</p> <ul style="list-style-type: none"> - 3 opinions, stating long-term health effect are unknown, with no proportions - 1 about unknown anecdotes from 47 events in total ever in the US - 1 general hypothesis, not about vaping - 1 possible association with a possible sign based on 42 young people - 1 stating 3 statements proven false in the abstract - 1 showing the same effect as its study on coffee - 1 not about CVD - 2 on active smokers - 1 that states it's probably possible for nicotine to have such effect but not in comparable products <p>(details in Contribution ID 4b10e139-2c3e-41fe-a12c-018d084cd94b and Contribution ID 0b027415-398b-4f46-a773-88a2a7a85fe1)</p> <p>Studies about recovering ex-smokers (that, as they stopped smoking, recover slowly like any ex-smoker) have been ignored. If vaping was a long-term CVD risk based on the same compound as in smoke, first of all the effect would be proportionate (and there are nearly 2 orders of magnitude of reduction, plus the most dangerous one in this perspective is absent), second of all there have been some hypotheses for a decade, and no evidence so far. Perhaps the precautionary principle in a continent</p>	The Opinion has been revised accordingly.

where millions smoke would be to reduce the risk as soon and as seriously as possible.

L15 and next you state weak to moderate evidence of carcinogenicity of the respiratory tract when you base most of the evidence on nitrosamines based on a paper on US products, not conforming to EU regulations, not adopting French AFNOR standards/certification, paper that doesn't pretend there are evidence of such risk. (details in Contribution ID ffa29d47-64cb-4e52-80bb-82c3de4ed3a5)

Please see table 1, answer 8.

L30 and next you state moderate evidence of systemic cardiovascular effects and carcinogenic risk without accounting for 2 orders of magnitude in reduction (amount) and based on direct risks that were based themselves on weak (to none) evidence. (cf. previous comments)

L42 and next, you state evidence of a gateway but ignored studies showing the opposite effect, including ones by prominent health actors and authorities of the EU. You also ignored the precautionary principle between a known risk (smoking) and a clearly considerably lower one (vaping) despite the example of snus. (details in Contribution ID c9c2edc8-f078-43e0-8959-97e28ef4c99a)

Please see table 1, answer 5.

L50 and next, you state weak evidence of smokers quitting with vaping despite national data from countries with a neutral or positive attitude on vaping show vapers account for a large part of the surplus of ex-smokers. And ignored so many studies that a Cochrane review published at the same time found moderate evidence of the superiority (!) of vaping with nicotine on commonly recommended options for smokers. (details in Contribution ID 8098daa0-c1a6-40d7-bc2c-3af7e1118702) We kindly ask you to review your report taking into account what could happen if, based on such Preliminary Opinion, the EU authorities missed or reduced slightly the opportunity to reduce smoking and to offer an option with a fraction of the risk if any serious risk at all. By having a neutral attitude about a product category, like on any other common goods, some countries already reduced considerably the future burden of diseases caused by smoking.

Please see table 1, answer 1.

455 Farsalinos ABSTRACT
Konstantinos, University of Patras, Greece

Lines 7-37.
The conclusions on the health effects of e-cigarettes seem to be misleading and out of context. The major issue related to the whole approach of the report is that it fails to acknowledge that the vast majority of e-cigarette (particularly regular/daily) users in the EU are current or former smokers [1,2]. An analysis of the 2017

Please see table 1, answer 1.

Eurobarometer survey found that, compared to never e-cigarette use, daily e-cigarette use was associated with 5-fold higher odds of being a former smoker of ≤ 2 years and 3-fold higher odds of being a former smoker of 3-5 years [3]. By reviewing the available evidence, some of which has been omitted in this report, it is expected that smokers will experience significant health benefits by switching from smoking to e-cigarette use. The conclusions are particularly problematic for the long-term systemic effects on the cardiovascular system and for carcinogenicity, both in the assessment of direct and second-hand exposure effects. Lines 42-47.

The conclusion on the strong evidence about gateway-to-smoking effects of e-cigarettes is fundamentally wrong because the authors have failed to acknowledge the common liability model as the most likely explanation for the observed effects. The strong reduction in youth smoking prevalence during the period of growing e-cigarette use experimentation in the US provides further evidence that the common liability model can better explain the research findings [4]. From 2011 to 2019, smoking rates decreased by 46.5% in US middle school students and by 63.3% in US high school students [4].

Ref:

1. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction*. 2016 Nov;111(11):2032-2040. doi: 10.1111/add.13506.
2. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Prevalence and correlates of current daily use of electronic cigarettes in the European Union: analysis of the 2014 Eurobarometer survey. *Intern Emerg Med*. 2017 Sep;12(6):757-763. doi: 10.1007/s11739-017-1643-7.
3. Farsalinos KE, Barbouni A. Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries. *Tob Control*. 2020 Feb 3:tobaccocontrol-2019-055190. doi: 10.1136/tobaccocontrol-2019-055190.
4. US Centers for Disease Control. Youth and tobacco use. September 9, 2020. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm

Please see table 1, answer 5.

456 Conley Gregory,American ABSTRACT

Lines 7-28: Studies from around the globe consistently report that frequent users of vaping products are almost exclusively smokers or ex-smokers, yet in summarizing potential health impacts for

Please see table 1, answer 1.

Vaping
Association,
United States

users of vaping products, the abstract makes no attempt to recognize the differences in toxicology, poisoning / injuries, cardiovascular effects, potential and known carcinogenicity, etc. between vaping products and combustible tobacco products. This does readers and policymakers a great disservice. The authors may wish to live in a world where cigarette smoking is not killing millions of people worldwide, but we do and it is wholly unhelpful to consider hypothetical health risks of vaping products without comparing those predicted risks to the very well-established health risks of combustible tobacco products.

457 Compernelle
Thomas, British
American
Tobacco,
Belgium

ABSTRACT

The conclusions of SCHEER's Preliminary Opinion lack objectivity, omitting the 'most recent scientific and technical information available'.

The Opinion finds strong evidence for risks of long-term systemic effects on the cardiovascular system, moderate evidence for local irritative respiratory damage, and weak to moderate evidence of carcinogenicity of the respiratory tract. This is in contrast with the widespread available published scientific evidence. SCHEER have not considered positioning e-cigarette effects relative to cigarettes, which is supportive of their reduced risk profile, since they expose users and bystanders to reduced toxicant levels compared to smoking (1-2). There is little evidence nicotine is a risk factor for long-term cardiovascular disease (3-4). Studies have shown smokers who switch to e-cigarettes have significant improvements in their vascular function, with measurable effects in as early as 1 month (5). E-cigarette use has been shown to improve the outcome (harm reversal) from smoking in COPD (chronic obstructive pulmonary disease) patients (4). E-cigarettes have significantly lower levels of toxicants compared to cigarette smoke (6) and have been estimated to have cancer potencies less than 1% of tobacco smoke (7). Public health agencies such as the WHO's International Agency for Research on Cancer state nicotine does not cause cancer (8-14).

The Opinion finds moderate and weak to moderate evidence that second-hand vapour is a cause of local irritative damage to the respiratory tract and cancer and cardiovascular disease, respectively. Independent studies from medical and health associations, including the British Medical Association (15), conclude that emissions and second-hand vapour from e-cigarettes do not present any significant health risks to bystanders, with negligible levels of air pollutants compared to cigarette smoke (1,16-18). The excess life cancer risk from second-hand vaping has been estimated as 10,000 times lower than from second-hand smoking (19).

Regarding cardiovascular effects, the Opinion has been revised.

Please see table 1, answer 1.

Please see table 1, answer 4.

The Opinion claims strong evidence e-cigarettes are a gateway to smoking for young people. Comprehensive studies have criticised ‘gateway’ arguments made in relation to e-cigarettes and found no reliable evidence of a gateway effect (1,2,20).

Please see table 1, answer 5.

While they are neither authorized nor marketed as cessation devices, several studies have shown e-cigarettes are effective in helping adult smokers quit smoking successfully (21-31), yet SCHEER infer the evidence available is weak. According to independent organisations, millions of smokers around the world have switched to using e-cigarettes (1,2,12,31-33). A recent study of 13,057 subjects from 28 EU countries found that compared with former smokers who never used e-cigarettes, daily e-cigarette users were 5 times more likely to have quit smoking (34). In the EU, 6 out of 10 people reportedly took up e-cigarettes to stop or reduce tobacco use (35).

Please see table 1, answer 6.

Finally, the Opinion proposes there is strong evidence flavours contribute to the attractiveness of e-cigarettes. Numerous public health bodies, including WHO, have recognised the importance of flavours in vaping products to act as a satisfactory alternative to cigarette smoking (37-39). Cigarettes are arguably the ‘most appealing, most addictive, and most toxic’ nicotine product (40-42) available. If smokers switch to e-cigarettes, this would be in the interest of and benefit to public health (40,43,44). We respectfully request SCHEER to reconsider their conclusions, referring to evidence provided.

Please see table 1, answer 7.



C1R0_- Abstract_References.pdf

458 CHARVA ABSTRACT
LOS
EKATERI
NA, IASO,
OBSTETR
ICS
GYNECO
LOGY,
PEDIATRI
CS,
RESERAC
H AND
GENERA

The SCHEER’s Preliminary Opinion focuses mainly on the assessment of e-cigarettes’ health effect compared to non-smoking and not continuous smoking. This does not provide the full spectrum of potential benefits and can lead to decisions that do not promote Public Health.

Please see table 1, answer 1.

It is not negotiable that Smoking Cessation is the best option for smokers and doctors should make every effort to help in this direction BUT in the reality there is a significant percentage of people that cannot quit even if they have tried several times with or without medical help.

There is a large body of evidence demonstrating that e-cigarettes

L
HOSPITA
L, Greece

are less harmful compared to continued smoking. For example a recent publication from a well-recognized smoking cessation center in Greece have shown that switching to electronic cigarette for 4 months has a neutral effect on platelet function while it reduces arterial stiffness and oxidative stress compared to tobacco smoking (Ikonomidis 2020 Effects of electronic cigarette on platelet and vascular function after four months of use).

Ref:

Ikonomidis 2020 Effects of electronic cigarette on platelet and vascular function after four months of use. Food and Chemical Toxicology. Volume 141, July 2020, <https://doi.org/10.1016/j.fct.2020.111389>

459 Willers ABSTRACT

Stefan, Department for Respiratory Medicine and Allergology, Lunds University, Sweden

Page 2 lines 43-44
One of the conclusions of the SCHEER's opinion is that "there is strong evidence that electronic cigarettes are a gateway to smoking for young people". The term gateway implies that there is a causal relationship between the use of e-cigarettes and the transition to cigarette smoking and that the use of e-cigarettes will lead to smoking among people who would otherwise not have smoked. Most studies on the topic comes from the US and circumstances in the US are not directly transferable to a EU context, as that the regulatory environment in the US is different from the countries where TPD2 has been implemented.

Please see table 1, answer 5.

In the 2020 Public Health England evidence report on e-cigarettes (Vaping in England 2020) the authors conclude that the evidence do not support that e-cigarettes are used extensively by youth who would otherwise not have smoked but rather find that the use is confined mostly to those who are smoking: "current vaping is mainly concentrated in young people who have experience of smoking. Less than 1% of 11- to 18-year-olds who have never smoked are current vapers" and "the data presented here suggest that vaping has not undermined the declines in adult smoking"

To state a gateway effect, it is not just necessary to find a relationship between the use of e-cigarettes and the initiation of smoking but also to find a causation. Most of the studies included in the SHEER opinion do not provide evidence of a causative relationship. In 2020 the Swedish governmental agency Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) published a report based on a systematic review on e-cigarettes and smoking initiation (Samband mellan snus och e-cigaretter och tobaksrökning/Association between the use of snus moist tobacco and e-cigarettes and tobacco smoking) the conclusions were: "It is probable that experimentation with e-cigarettes may be a predictor for later initiation of cigarette smoking (certainty of evidence moderate). The certainty of evidence was higher among young individuals

(certainty of evidence moderate) but could also be found among adults (certainty of evidence low). Association between experimentation with e-cigarettes and current use of cigarettes was also found (certainty of evidence moderate).” And “Based on the results of this systematic review, it is not possible to determine whether the associations found in the material are causal, or mainly statistical relationships. In most of the included studies, it is possible that confounders affect the outcome”

The SBU report supports an association, but is not supportive of a gateway effect, even if it does not rule it out. The question on if there are a causative gateway effect or not should be subject to further research. The statement in the SHEER report “there is strong evidence that electronic cigarettes are a gateway to smoking for young people” should thus be moderated to “there is moderate-strong evidence that electronic cigarettes are associated with smoking for young people, but given the current evidence it is impossible to conclude if the relationship is causative or not”

460 Guiton ABSTRACT
Pascal, Onl
y, France

We welcome SCHEER’s efforts to assess the topic of vaping in the context created by the TPD in the EU, prior to possible discussions on its revision. However this draft report fails to provide an adequate assessment in the European context on several points:

- 1) It does not make a relative risk assessment between vaping and cigarettes when almost all vaping users in the EU are or have been smokers (McNeill, 2018 ; Farsalinos 2016);
- 2) A large part of the studies cited concern products from outside the EU market; or, do not distinguish between uses with or without nicotine (or otherwise); and come from regulatory context radically different from that created by the TPD;
- 3) Some important European studies are not reviewed;
- 4) Another gap in relation to its mandate, the SCHEER draft never addresses the impact of regulations and/or actions of authorities on the issues addressed (Hua-Hie Yong, 2017 ; Ward, 2020). It would have been desirable the Scientific Committee analysed risks produced by the different national implementations: evolution of smoking prevalence and evolution of the risks linked, between country tolerant to vaping, e.g. France, and country stigmatising vaping, e.g. Spain; the effects of ban flavours and high taxes, e.g. Estonia, and the risks associated with the creation of a vast black market out of control.

On the abstract text itself, we note:
[p. 2 l. 14] The data presented in the report do not seem to allow asserting

Please see table 1, answer 1.

Please see table 1, answer 8.

Please see table 1, answer 2.

This was outside the scope of the Opinion.

The Opinion has been revised accordingly.

strong evidence of systemic cardiovascular effects (Benowitz, 2016 ; Shahab, 2017). [p.2 l.16] & [p.2 l.37] Data for products marketed under the TPD regime, which is the subject of this report, cannot support a carcinogenic risk by nitrosamine accumulation. Nicotine used in the EU is a highly purified grade (TPD art. 20 §3.d, 2014). This point indicates a more general confusion in the heterogeneous data used by the SCHEER, who does not seem to have discriminated the relevant data for specific European situation created by TPD.

Please see table 1, answer 4.

[p. 2 l. 42 ss] The gateway hypothesis is not supported by the evidence presented in this report. The studies presented suffer from critical problems, including a lack of consideration of the risk co-factor of parental smoking and friends smoking, high attrition bias, etc. (Chan et al. 2020). The main meta-analysis presented has authors' self-report bias. The scientific criteria for validating a causal hypothesis as the gateway theory are not met (Etter, 2017). More robust European studies, notably the OFDT study in France, show effects incompatible with this hypothesis (Chyderiotis, 2019). All this chapter and conclusion need to be completely revised.

Please see table 1, answer 5.

[p. 2 l. 49 ss.] Many data were not included in the report. Cochrane review found 50 clinical studies and conclude to moderate-certainty evidence vaping with nicotine increase quit rate compared to NRT (Hartmann-Boyce, 2020). Preliminary results from other clinical studies (Eisenberg, ACC.20) are in the same direction. Santé Publique France has demonstrated that at least 700,000 people have quit smoking in a consolidated way thanks to vaping before 2017 (Pasquereau, 2017). Based on the Eurobarometer 429, an estimated 6 million EU citizens had quit with the help of vaping in 2014 (Farsalinos, 2016). The Smoking Toolkit Study showed that smoking cessation increased by ~70,000 net additional successful quitters thanks to vaping in 2017 in England (ASH, 2020). etc.

Please see table 1, answer 6.

We recommend a thorough and rigorous revision of the draft report before its transmission to the Commission.

461	Clark Alex, The Consumer Advocates for Smoke-free Alternative	ABSTRACT	Pg. 2	Lines 42	-	44
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Following decades of research “gateway” remains a hypothesis. Suggestions that use of one substance increases the likelihood of using a specific and more risky substance has more political value than scientific relevance. Poly-use best describes people’s relationship with drug use. “Among youth who reported any past 30-day tobacco or e-cigarette use, poly-use was the dominant

Please see table 1, answer 5.

	s Associatio n (CASAA), United States		pattern of use. Tobacco-naïve youth rarely reported using e-cigarettes, and most e-cigarette users were ever users of other tobacco products.” (Collins, et al, 2017) Ref: Collins, Lauren K, et al. “Frequency of Youth E-Cigarette, Tobacco, and Poly-Use in the United States, 2015: Update to Villanti Et Al., ‘Frequency of Youth E-Cigarette and Tobacco Use Patterns in the United States: Measurement Precision Is Critical to Inform Public Health.’” Nicotine & Tobacco Research, vol. 19, no. 10, 2017, pp. 1253–1254., doi:10.1093/ntn/ntx073.	
462	Tsitsimpik ou Spetseris Christina Independe nt Authority for Public Revenue, Greece	ABSTRACT	1-57	The contribution does not included any comment.
463	Balsam Pawel, Warsaw Medical university, Poland	ABSTRACT	The document doesn’t include any information on Heat not Burn products. Those are registered by FDA as modified risk tobacco product (IQOS). It may be used as a product to quit smoking. Another thong is fact, that it causes much smaller Indoor Pollution: Comparative Indoor Pollution from Glo, Iqos, and Juul, Using Traditional Combustion Cigarettes as Benchmark: Evidence from the Randomized SUR-VAPES AIR Trial Mariangela Peruzzi 1,2,* ,† , Elena Cavarretta 1,2,† , Giacomo Frati 1,3, Roberto Carnevale 1,2 , Fabio Miraldi 4, Giuseppe Biondi-Zoccai 1,2, Sebastiano Sciarretta 1,3, Francesco Versaci 5, Vittoria Cammalleri 6, Pasquale Avino 7 , Carmela Protano 6 and Matteo Vitali	Please see table 1, answer 6. Please see table 1, answers 1 and 4.
464	Sproga Maris,Sm ke Free Associatio n of Latvia,Lat via	ABSTRACT	Page 2, lines 7- 40 Its important to look detailed into assessment of health impacts of e-cigarettes compared to smoking. As for now, it focuses only on health impacts when to compare with non-smoking. Its not true - cigarettes are mainly used as alternatives to smoking cigarettes. Science demonstrates that e- cigarettes are less harmful compared to smoking. For example, the Tobacco Advisory Group of the U.K.’s Royal College of Physicians, concluded the following in the report “Harm reduction in nicotine addiction: Helping people who can’t quit”, Oct. 2007,	Please see table 1, answer 1.

“Since nicotine is the primary addictive constituent of tobacco smoke, the harm reduction approach for those who cannot otherwise quit smoking tobacco or who want to reduce the impact their smoking has on themselves and others is to substitute cigarettes with less hazardous alternatives. Even though smoking-related harms may be merely reduced rather than removed by this approach, many lives could also be saved and much morbidity prevented.” Its vital to mention this in the SCHEERS opinion.

Please see table 1, answer 6.

<https://cdn.shopify.com/s/files/1/0924/4392/files/harm-reduction-nicotine-addiction.pdf?15599436013786148553>

Page 2, lines 43-44
SCHEER’s opinion states that “there is strong evidence that electronic cigarettes are a gateway to smoking for young people”. Its mainly an opinion based in the United States. We need to look for EU based evidence. Also, SCHEER’s opinion recognizes that e- cigarettes available in Europe differ frequently from those available in the U.S., including a lower maximum nicotine concentration in the EU and stricter regulatory provisions. The available information from European countries (the Netherlands, UK, France, Germany) does not support the conclusion of a strong evidence that e-cigarettes are a gateway to smoking.

Please see table 1 answers 1 and 11.

https://www.dkfz.de/de/tabakkontrolle/download/Publikationen/sonstVeroeffentlichungen/2020_E-Zigaretten-und-Tabakerhitzer-Ueberblick.pdf

Page 2, lines 50-51
SCHEER mentions that “there is weak evidence for the support of electronic cigarettes' effectiveness in helping smokers to quit”. Its not like that – and it can be found in many recent publications, stating the contrary. For instance, the UK National Health Services (NHS) advises on their website Using e-cigarettes to stop smoking and concludes that “Many thousands of people in the UK have already stopped smoking with the help of an e-cigarette. There's growing evidence that they can be effective.” (<https://www.nhs.uk/live-well/quit-smoking/using-e-cigarettes-to-stop-smoking/>). Such an evidence should also be taken into account.

Please see table 1, answer 6.

465 Olteanu Vlad, Juul Labs Inc., Belgium ABSTRACT

Initially, there are several inconsistencies between conclusions in the abstract and the conclusions in the more in-depth analysis in the body of the report. The impact of this cannot be overstated given the importance of an abstract -it is the part of a scientific report that is most visible. A 1987 editorial by the editors of Obstetrics and Gynaecology noted that what the reader “deserves to be told is some indication of the report's purpose, methodology, and implications.” The SCHEER abstract does not do this.

An example of an inconsistency is where the abstract states that “the overall weight of evidence for risks of local irritative damage to the respiratory tract is i) moderate for heavy users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine, and ii) not to be excluded for average and light users. However, the overall reported incidence is low.” (pg 2, ln 9; emphasis added). This conclusion is at odds, however, with the text of the health effects section of the report which states that “If assessed, acute mouth / throat irritation, and cough are reported by a sub-group of users (Polosa et al., 2011; Palamidis et al., 2017) and that these effects are not attributed to the nicotine content (Palamidas et al., 2017). These effects are in fact thought to be caused by hyperventilation, which is associated with long puffing time (Morjaria et al., 2011).” (pg 47, ln 13; emphasis added) More egregious is the discrepancy between the conclusion in the abstract that “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong,” (pg 2, ln 13) and the statement within the text of health effects section, where it actually says the European Heart Network (EHN) concluded that ...’the long-term effects on the cardiovascular system are still unknown due to the lack of relevant data” (pg 47, ln 28-36). Inconsistencies between the abstract and in-depth analysis coupled with the fact that most readers will only read the abstract, and not the longer report, increase the chances that inconsistent conclusions will be amplified by individual readers and media but, perhaps also by policymakers tasked with reconciling this scientific opinion with public health interests. Scientific abstracts disproportionately influence media press releases and coverage.

Regarding cardiovascular effects the Opinion has been revised.

An abstract should act as an introduction and review of the entire document. If intended to act as a standalone entity, it should include information regarding the background, purpose, results, and contents of the work. This abstract does not include any of these necessary details, but instead presents a list of conclusions without any context. This is at odds with other public health agency reports that do not provide an abstract but focus on a more detailed summary of each section at the front of the report. We recommend that the committee focus the abstract on the report’s purpose, methodology, and implications and reserves discussion of the conclusions to a longer summary similar to previous comprehensive reports such as PHE and NASEM (uploaded with this submission in full (as .pdf) or as a first page .jpg file –for reference purposes -where a full upload was not possible because of the 1MB file size upload limitation or because of copyright rules).

The Abstract summarizes many of the issues explored in more depth in the body of the Preliminary Opinion. We have provided substantive comments on those sections, but note here that this section is one of the three sections

466 Woessner ABSTRACT
Julie, Intern
ational

Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU

(Abstract, Summary, Scientific Opinion) that many, if not most, people will rely upon to gain an understanding of SCHEER's findings. Therefore, the selection of the information to be contained in this section is crucial to avoid misleading or misinforming readers.

Page 2 / Lines 9-12
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is moderate. The low incidence should be emphasized too.

Page 2 / Lines 13-14
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is strong.

Page 2 / Lines 15-17
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak to moderate.

Page 2 / Lines 17-19
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak.

Page 2 / Lines 20-21
The bold emphasis is misleading because it gives the impression that the risk itself is strong. In this case it's highly misleading because the Abstract fails to reflect the other part of this risk assessment in the Scientific Opinion as found at page 13 line 34; page 54, line 48 ("Therefore, the related risk is low."); and page 62, line 8 ("Therefore, the risk is expected to be low.")

Page 2 / Lines 31-32
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is moderate. In this case it's especially misleading because the third line of evidence found in the SCIENTIFIC OPINION section page 16, lines 9-10 states: "Exposure of second-hand exposed persons to glycerol or aldehydes is negligible or orders of magnitude lower than for electronic cigarette users." This important information should be present in the abstract.

Please see table 1, answer 4.

Page 2 / Lines 33-35
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak to moderate.

Please see table 1, answer 3.

Page 2 / Lines 36-37
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak to moderate.

Page 2 / Lines 42-47
We question how SCHEER ends up with such a strong opinion on a gateway hypothesis when the evidence is so weak in the EU and in the US. See our comment in TERMINOLOGY on the gateway hypothesis.

Please see table 1, answer 5.

Page 2 / Lines 49-52
We question how SCHEER and the 2020 Cochrane Review, within basically the same timeframe, and with basically the same data at their disposal, end up with such different opinions. See our comments in 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use.

Please see table 1, answer 6.

467 No agreement to disclose personal data ABSTRACT

ANAFE – Confindustria is the national trade association that has been representing the Italian industry of electronic cigarettes since 2013. ANAFE, which brings together the majority of Italian firms producing devices and e-liquids, has carefully examined the preliminary Opinion on electronic cigarettes drawn up by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER). Before proceeding with the specific comments related to the sections of the preliminary opinion, it is crucial to outline some general comments.

First of all, ANAFE believes that the opinion, although accurate and detailed in some sections, is not particularly updated and fully relevant to the European context. For instance, most of the data and studies considered happen to be too old (some of them refer to 4 or even 5 years ago) or in contrast with technological developments and market developments.

Please see table 1, answers 2, and 11.

Furthermore, a lot of studies are related to the American market and - as noted later in the submission - lead to conclusions that should not be inferred for the European market too, considering the key differences between the two. This issue is particularly relevant when it comes to young people and the role of e-cigs as a gateway to smoking. On this point, we would like to highlight here the specific case of the Italian market. Data

Please see table 1, answers 8 and 5.

from the latest Blue Book of the Italian Customs Agency show that the SCHEER hypothesis on the role of e-cigs as a gateway to smoking looks to be inferred by the principle of maximum precaution, rather than evidence-based. As a matter of fact, despite the greater presence of nicotine-based products on the market in the last years, such data show that the overall number of consumers has not increased. Similarly, in the American market there is no corresponding increase in the number of adult smokers compared to data on young e-cigarettes' users.

Considering the issues brought about by the SCHEER, ANAFE believes that, overall, the current relevant Directive, in force since 2014, effectively defines the European legislative framework for e-cigarettes and that a harmonized system of rules is the most adequate approach for the protection of European consumers. Moreover, Member State's discretionary powers within the scope of the Directive, allow for a better combination of national fiscal and health policies in the fight against smoking. On the contrary, strict European level provisions would clash with specific national features, such cultural factors and affect the national health systems, which in the end bear the costs of smoking.

In this regard, ANAFE would like to emphasise here that the transposition of Directive 2014/40/EU in the Italian legislative framework has been carried out with a particular focus on the protection of vulnerable consumers and the adoption of an incisive sanctions system. In particular, legal provisions have been adopted - among others - aimed at decisively punishing manufacturers / retailers of products that are not compliant with the Directive, as well as retailers who sell e-liquids (with and without nicotine) to minors. Moreover, in Italy, e-liquids containers, with and without nicotine, can only be purchased through "authorised channels", and, in particular, from retailers with specific authorisation and strict subjective and objective requirements. In conclusion, ANAFE believes that the current European legislative framework effectively regulates electronic cigarettes and liquid refill containers' market, while leaving Member States the possibility to adopt the most suitable provisions to address the specific feature of their respective national markets.

468 Pooler
Marc,UK
Vaping
Industry
Associatio
n,United
Kingdom

ABSTRACT

The UK Vaping Industry Association (UKVIA) strongly believes adult smokers around the world should have appropriate access to less harmful alternatives to smoking such as vape products. We fully support evidence-based regulation highlighting the public health potential of vaping products and the life changing impact they have had on adult smokers quitting cigarettes.

- The abstract of the SCHEER Preliminary Opinion on Electronic

Please see table 1, answer 1.

Cigarettes is neither informative nor fit for purpose. An abstract should be clear, concise, unbiased and reflect the contents of the report it describes.

- It does not contain the information one would normally expect to see in an abstract for a report of this size such as background, objectives and results.
- The abstract takes the form of a list of conclusions stated as being supported by a weight of evidence that is rated ‘low’, ‘moderate’ etc. There is no explanation in the report, including in the methodology, as to what these ratings mean and how they were determined.

- Some of the conclusions presented in this abstract are at odds with the information and conclusions in the main body of the report. For example, page 2, line 13 of the abstract states that the overall weight of evidence for long-term effects on the cardiovascular system, are strong. Page 47, line 28 – However, in the body of the report, a European Heart study is cited as concluding that ‘the long-term effects on the cardiovascular system are still unknown due to a lack of relevant data’.

- The abstract is the most visible part of the report, so inconsistencies between the abstract and main body of the report increase the likelihood that inappropriate erroneous conclusions will disproportionately influence readers of this report.

Please see reply to coment 440.

469 Moiroud ABSTRACT
Jean,Fédération
ation
Interprofes
sionnelle
de la Vape
(FIVAPE),
France

P. 2, lines 7-37: a revision of the preliminary report is needed in order to take into account new and relevant contributions on health effects of e-cigarettes.

Please see table 1, answers 2 and 11.

P. 2, lines 15-19: The only references that deal with a carcinogenic effect of e-cig concern high levels of nitrosamines, formaldehydes and acetaldehydes. This data seems to be generated from very specific “macerated” e-liquids or heated tobacco. It is not commonly found in the European market e-liquid standards. Moreover, these levels are still very far from those found in tobacco cigarettes.

Please see table 1, answer 4.

P. 2, lines 46-47: this statement is partially wrong, flavour also has an important contribution for smoking cessation, as shown in this recent study:

Please see table 1, answer 7.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

ref:
Friedman AS, Xu S (2020). Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation.
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

470 Cattaruzza Maria Sofia, Italian Society of Tobaccoogy SITAB, Italy

ABSTRACT

ABSTRACT: please explicitly refer to the “aerosol” emitted from e-cigarettes in the abstract and in the text.
Examples
Abstract line 30: “second-hand exposed persons” could be: “second-hand aerosol exposed persons”
Section 6.5.2.2 pag 31 line 29 “Second-hand exposure” could be “Exposure to second-hand aerosol”
Section 6.5.2.3 pag 38 line 14 “Second-hand exposure” could be “Exposure to second-hand aerosol”
Section 6.5.2.3 pag 39 line 10 “Conclusion on second-hand exposure” could be “Conclusion on exposure to second-hand aerosol”

Thank you for your suggestion.

471 't Hart Emil, Elektionische Sigaretten Bond Nederland (Esigbond), Netherlands

ABSTRACT

Page 2 lines 7-40
The SCHEER’s opinion does not address the role that e-cigarettes can play in reducing the harm caused by smoking for those that fully switch because it is only focusing on the relative risk of using electronic cigarettes compared to non-smoking. As e-cigarettes are primarily used as an alternative to smoking, we can conclude that the approach in the opinion does not reflect the reality. If we focus on the Dutch data, for example, the Dutch Health Authority Trimbos Institute concluded in her factsheet ‘Kerncijfers Roken 2019’ that the group of e-cigarettes users almost exclusively consists of (ex) smokers because only 0.2% of those e-cigarette users have never smoked before that time.

Please see Table 1, answer 1.

There is broad scientific consensus that electronic cigarettes are less harmful compared to continued smoking. This is endorsed by the Dutch State Secretary, on April 26th 2020, in his answering to questions in parliament in response to the National Prevention Agreement, in which he states: ‘There is indeed broad consensus’ ... ‘that an individual smoker who switches completely to using an e-cigarette has less health risks than a smoker who continues to smoke’.
(p.49)

Finally, external expert of the currently tabled SCHEER's opinion, and health expert of the Dutch National Institute of Public Health and Environment (RIVM), Dr. R. Talhout, as co-author of a recently published article in the 'International Journal of Environmental Research and Public Health' reiterated that the electronic cigarette can play a role in reducing the harmful effects of smoking and emphasized the need to promote the benefits of the e-cigarette and the disadvantages of the traditional cigarette, by stating that: 'Although total cessation of nicotine and tobacco products would be most beneficial to improve public health, exclusive e-cigarette use has potential health benefits for smokers compared to cigarette smoking.'... 'By targeting the identified distinguishing factors, health communication strategies can stress the pros of e-cigarettes and the cons of cigarettes for smokers and dual users.'

By fully focusing your assessment on the relative risk of using electronic cigarettes compared to non-smoking, while 99.8% of the Dutch e-cigarette users are (ex) smokers, the opinion misses to address the role that e-cigarettes can play in reducing the harm caused by smoking for those that fully switch. The Dutch e-cigarette association for e-cigarette distributors and specialty stores (Esigbond), therefore, call on the SCHEER committee to also investigate how the e-cigarette can contribute to reducing the harmful effects caused by smoking.

Page 2 lines 43-44
In the SCHEER's opinion it is concluded that "there is strong evidence that electronic cigarettes are a gateway to smoking for young people". However, from the Dutch available data, we can conclude that for the Netherlands there is strong evidence that electronic cigarettes are not a gateway to smoking. In that regard the Dutch Health Authority Trimbos Institute concluded in her factsheet 'Kerncijfers Roken 2019' that regular e-cigarette use among adults is low with 1.6% - a group that almost exclusively consists of (ex)smokers because only 0.2% of those e-cigarette users have never smoked before that time. This is in line with earlier published data by Trimbos in 2017 that 'Only few smokers (3%)

Please see table 1, answer 5.

have used an e-cigarette before smoking’. Finally, the most recent Trimbos data shows that there is limited regular use among young people: only 1 in 10 young people who use the e-cigarette do that ‘almost every week or more’. This is consistent with earlier research by Trimbos, which shows that few young people use the electronic cigarette regularly: 2 percent daily and 3 percent weekly.

References:

Trimbos Instituut (juli 2020) Kerncijfers Roken 2019: de laatste cijfers over roken, stoppen met roken en het gebruik van elektronische sigaretten.

Beantwoording Kamervragen staatssecretaris Blokhuis - Nationaal Preventieakkoord (26 april 2020) (p. 49)

Romijnders, K.A. et.al. E-Liquid Flavor Preferences and Individual Factors Related to Vaping: A Survey among Dutch Never-Users, Smokers, Dual Users, and Exclusive Vapers. Int. J. Environ. Res. Public Health 2019, 16, 4661.

Trimbos Instituut (juli 2020) Kerncijfers Roken 2019: de laatste cijfers over roken, stoppen met roken en het gebruik van elektronische sigaretten.

Trimbos Instituut (2017) Nationale Drug Monitor

472 Pooler
Marc,UK
Vaping
Industry
Associatio
n,United
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ABSTRACT

The UK Vaping Industry Association (UKVIA) strongly believes adult smokers around the world should have appropriate access to less harmful alternatives to smoking such as vape products. We fully support evidence-based regulation highlighting the public health potential of vaping products and the life changing impact they have had on adult smokers quitting cigarettes.

Please see table 1, answer 1.

- The abstract of the SCHEER Preliminary Opinion on Electronic Cigarettes is neither informative nor fit for purpose. An abstract should be clear, concise, unbiased and reflect the contents of the report it describes.
- It does not contain the information one would normally expect to see in an abstract for a report of this size such as background, objectives and results.
- The abstract takes the form of a list of conclusions stated as being supported by a weight of evidence that is rated ‘low’, ‘moderate’ etc. There is no explanation in the report, including in the methodology, as to what these ratings means and how they were determined.
- Some of the conclusions presented in this abstract are at odds with the information and conclusions in the main body of the report. For example, page 2, line 13 of the abstract states that the overall weight of evidence for long-term effects on the cardiovascular system, are

strong. Page 47, line 28 – However, in the body of the report, a European Heart study is cited as concluding that ‘the long-term effects on the cardiovascular system are still unknown due to a lack of relevant data’.

- The abstract is the most visible part of the report, so inconsistencies between the abstract and main body of the report increase the likelihood that inappropriate erroneous conclusions will disproportionately influence readers of this report.

473	Mark Oates, We Vape UK, United Kingdom	ABSTRACT	<p>The abstract on page 2 line 13-14 suggests that there is "evidence for risks of long-term systemic effects on the cardiovascular system is strong"</p> <p>We know that the risks around cardiovascular systems comes from Carbon Monoxide and not nicotine. Studies attached suggest that with both Snus and Nicotine Replacement therapy there is no known increase in risk to the cardiovascular system from nicotine.</p> <p>Ref: Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies (Jansson et al., 2012) Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death (Hubbard et al., 2005)</p>	The Opinion has been revised accordingly.
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474	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	ABSTRACT	<p>Page 2 lines 7-40</p> <p>The SCHEER opinion considers electronic cigarettes with regard to the risks of their use with non-smoking. Electronic cigarettes serve in many cases as an alternative to smoking. There is significant number of evidence that electronic cigarettes are less harmful than smoking. This has been well described by the Royal College of Physicians of London (RCP) in its thorough April 2016 report and more recently by McNeil et al. (2018) in a report to Public Health England. https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review/evidence-review-of-e-cigarettes-and-heated-tobacco-products-2018-executive-summary</p>	Please see table 1, answer 1.
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For example, on the subject of relative risk, based on smoke and vapour toxicology the RCP stated: "Although it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure".

Page 2 lines 43-44
I am not aware of any available studies relevant to the EU market that provide convincing evidence that e-cigarettes are a gateway to smoking for adolescents. The SCHEER report contains data, coming from the U.S. market, not EU. However, electronic cigarettes available on the US market differ from those available in the EU, as the regulation of these products itself. Moreover, the available evidence from the EU does not support the statement that electronic cigarette are a gateway to smoking.

Please see table 1, answer 5.

Page 2 lines 50-51
I consider e-cigarettes to be a significant benefit in the fight to reduce deaths. From a therapeutic point of view, the use of nicotine in alternatives such as e-cigarettes is certainly the best ways for those who fail to quit smoking.

As was stated in the letter: Letter from 36 International Experts and Academics in Tobacco Control On Tobacco Harm Reduction and the Dutch National Prevention Agreement the subject of smoking cessation, 2019

<https://www.clivebates.com/documents/NLLetterMarch2019.pdf>
there is increasing evidence from Randomised Controlled Trials (RCT) that have been designed specifically to explore effects on tobacco smoking, that vaping products (e-cigarettes) can help smokers to stop smoking. A Cochrane review published in 2016 concluded that smokers using an e-cigarette were more likely to quit compared to those using a placebo at 6 months. More recently, a RCT of e-cigarettes versus Nicotine Replacement Therapy (NRT) alongside behavioural support in England, reported an almost two-fold increase in 12 month quit rates with e-cigarettes.

Please see table 1, answer 6.

Ref:
Hajek (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. DOI: 10.1056/NEJMoa1808779
Hartmann-Boyce et al. (2020) Electronic cigarettes for smoking cessation (Review). Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD010216. DOI: 10.1002/14651858.CD010216.pub4.

475 Proaño ABSTRACT
Gómez
Isabel,Euro

See attachement.

Thank you for your views and your support.
As regards pulmonary toxicity, please see Table 1, answer 10.
Risk management is outside of the scope of the SCHEER.

pean
Federation
of Allergy
and
Airways
Diseases
Patients'
Associatio
ns,Belgium



EFA_Response_to_SC
HEER_opinion_on_e-c

476	Arnott Deborah,A ction on Smoking and Health,Uni ted Kingdom	ABSTRACT	<p>In summary there is evidence which has not been included in the Opinion which needs to be taken into account in the final report to inform a revised analysis of the weight of the evidence on the cardiovascular impact of e-cigarettes (P.2 13-14); effectiveness in smoking cessation(P.2 49-51); on gateway effect and the addictiveness of e-cigarettes, both of which are crucial to whether the impact of flavours on attractiveness and initiation are of significant concern (P.2 42-47).</p> <p>In addition SCHEER reaches no conclusions about the overall weight of evidence on the health effects both for e-cigarette users and for secondhand exposed persons, both of which are essential to properly inform the review of the EU TPD and whether any legislative amendments are required.</p> <p>To do this requires the quantification of risk in comparison with other benchmarks for other toxic substances for which one obvious comparison would be the EU occupational health exposure limits. https://echa.europa.eu/oel#:~:text=Occupational%20exposure%20limits%20(OELs)%20are,the%20air%20of%20a%20workplace.&text=OELs%20are%20mainly%20intended%20to,as%20vapours%2C%20mists%20or%20dusts.</p> <p>It also requires an assessment of the relative risk of e-cigarettes and smoking for primary users.</p> <p>E-cigarettes are not risk free, and are not recommended for use by never smokers. They have a role in public health insofar as they are used by smokers to quit smoking or cut down and ex-smokers to prevent relapse. For these populations relative risk is crucial. For</p>	<p>Please see table 1, answers 5 and 6. Regarding cardiovascular effects, the Opinion has been revised.</p> <p>The overall weight of evidence for users and second-hand exposed persons are described for different health effects in the Opinion.</p> <p>Please see table 1, answer 3.</p>
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example in setting out the carcinogenic risk of e-cigarettes SCHEER quotes from Stephens et al without including the assessment of relative risk which is 0.4%.

<https://pubmed.ncbi.nlm.nih.gov/28778971/>

Further the UK Government commissioned the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) a committee of independent experts that provides advice to Government on matters concerning the toxicity of chemicals in food, consumer products and the environment to review the evidence on e-cigarettes. The Committee's report published in September 2020 concluded that "In considering the comparison of E(N)NDS [nicotine and non-nicotine containing e-cigarettes] use with CC [conventional cigarette] smoking, the Committee concluded that the relative risk of adverse health effects would be expected to be substantially lower from E(N)NDS."

<https://cot.food.gov.uk/sites/default/files/2020-09/COT%20E%28N%29NDS%20statement%202020-04.pdf>

(NB files would not upload so I included links instead)

477 Oates ABSTRACT
Mark, We
Vape, United
Kingdom

ABSTRACT
Page 2 lines 42-44
Suggests that Vaping is a gateway to smoking. This is wholly wrong and Vaping is in fact a off ramp from smoking. Evidence from the Cochrane "Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose?" Study found vaping to be better than all other smoking cessation methods to help people quit smoking.

The British Medical Journal Study "Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross sectional survey data in England, Scotland and Wales" suggests that when considering whether the rise of vaping led to an increase or normalisation of combustible cigarettes. The study found there was no link to a normalisation of smoking in youth.

Please see table 1, answers 5 and 6.

The study: Considerations related to vaping as a possible gateway into cigarette smoking: an analytical review
Peter N Lee 1, Katharine J Coombs 1, Esther F Afolalu
Found: "A true gateway effect in youths has not yet been demonstrated. Even if it were, e-cigarette introduction may well have had a beneficial population health impact."

Ref:

1. https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used
2. <https://tobaccocontrol.bmj.com/content/29/2/207>
3. <https://pubmed.ncbi.nlm.nih.gov/31354936/>

478 Kuttruf Andrej, Vaping Global, United Kingdom

ABSTRACT

I'm surprised about the form, positioning and conclusions of this abstract.

700 000 smokers die every year from smoking in the EU. E-cigarettes are an increasingly popular new technology challenging the monopoly of cigarettes, with promising scientific evidence to be 'unlikely to exceed 5% of the harm of tobacco' (Royal College of Physicians, <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction>), yet the abstract doesn't draw any comparisons between cigarettes or e-cigarettes. Surely, having smokers switch away from one of the deadliest habits to a far less harmful alternative should be a desirable objective? Surely, e-cigarettes which stand in direct competition to cigarettes and have been statistically proven to reduce smoking rates by getting parts of the smoking population to switch (see UK smoking rates fastest declining in Europe, <https://digital.nhs.uk/data-and-information/publications/statistical/statistics-on-smoking/statistics-on-smoking-england-2019>), should be evaluated in their harmfulness in relation to cigarettes?

The abstract itself tries to give a view on the harm of e-cigarettes (for a non-smoker) by weighing potential risk factors. This is done in a clumsy and superficial way, though it fails to give a representative weighing of the risk in rates of incidence. It uses terms like 'low' and 'weak', which give the readers no way to quantify the actual risk. For example it states the risk of injuries

Please see table 1, answer 1.

Please see table 1, answer 3.

due to burns and explosion is 'strong' - 'however the incidence is low'. This is a crude misrepresentation. In the US with tens of millions of vapers, there were only 15 reported fires and explosions with e-cigarettes in 2015 according to the US National Fire Protection Association: <https://www.nfpa.org/News-and-Research/Data-research-and-tools/US-Fire-Problem/Smoking-Materials>

The conclusions in detail are dubious and in some instances completely against any statistical and scientific data.

There is no gateway effect to smoking as there is no material uptake of e-cigarettes by non-smokers. In the UK, one of the most developed markets of e-cigarettes with more than 3.2m vapers, only 0.8% of users of e-cigarettes were people who never smoked. On the contrary, most countries show a steeper decline in smoking rates as vaping rates increase (with the total between both populations still lower than historical smoking rates, leading to a net positive effect for public health).

Please see table 1, answer 5.

The abstract also concludes that there is weak evidence to support e-cigarettes' effectiveness in helping smokers to quit. This is against the scientific evidence supported by countless studies:

Please see table 1, answer 6.

'E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy', Hajek et al 2019, <https://www.nejm.org/doi/full/10.1056/NEJMoa1808779>

'There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT.', Cochrane Collaboration 2020, <https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>

'The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level.', Zhu S-H et al, 2018, <https://www.bmj.com/content/358/bmj.j3262>

For the policy maker, it is worth pointing out the conclusion of a wide scientific review of Royal College of Physicians:

'However, if [a risk-averse and precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly (...), then it causes harm by perpetuating smoking.' (Section 12.10 page 187), <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction>

479 RICHARD ACKNOWLEDG -- Lignes 13 et 14 -- Thank you for your comment.

Isabelle, Ludivape (unpaid site), France

MENTS

Les preuves actuellement disponibles sur une étude menée en 2014, indiquent que « les cigarettes électroniques sont de loin une alternative moins nocive au tabagisme » et que « des avantages importants pour la santé sont attendus chez les fumeurs qui passent du tabac aux cigarettes électroniques ».

Lien de l'étude de 2014 : <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/>

Après 3 ans de vapotage, et l'arrêt complet du tabac, mon cardiologue m'a fait stoppé tout mon traitement bêta-bloquant, m'indiquant que je n'avais plus aucun risque cardio-vasculaire puisque je ne fumais plus. Depuis maintenant plus de 7 ans que je vape, je n'ai jamais refait d'incident cardiaque. Ma tension est stable.

-- Lignes 42 à 44 --

Il n'existe aucune preuve que la cigarette électronique est une porte d'entrée vers le tabagisme. J'ai une fille qui a commencé à fumer à 14 ans. Si j'avais eu connaissance de l'existence de cette cigarette électronique, je l'aurais faite vapoter pour limiter les risques de maladies liées au tabac à 5%.

-- Lignes 49 à 51--

Il a été démontré par deux études dont liens ci-dessous, que l'utilisation d'une cigarette électronique augmente les chances de sevrer du tabagisme.

https://www.nejm.org/doi/full/10.1056/NEJMoa1808779?query=fatured_home

<https://www.mdpi.com/1660-4601/14/7/798>

Personnellement, j'ai essayé pendant une dizaine d'années, tous les substituts présents sur le marché sans aucun résultat. J'ai rencontré la vape fin 2012, et début 2013 je ne fumais plus. À ce jour c'est toujours le cas.

480 Aubert
Dominique
,VAP'
sas,France

ACKNOWLEDGMENTS

lines 13 and 14: this section indicates that the risks of cardiovascular problems due to vaporization are high.

However, a study conducted in 2014 to compare the "potential risks associated with the use of electronic cigarettes with the well-established devastating effects of smoking" explains in its conclusions that the currently available evidence indicates that "electronic cigarettes are by far a less harmful alternative to smoking" and that "significant health benefits are expected in smokers who switch to electronic cigarettes".

Lines 42 to 44: These lines note that steaming is a gateway to smoking.

However, a great deal of scientific work has already shown that no, steaming does not lead to smoking (Study no. 1 [2020], Study no. 2 [2016], Study no. 3 [2014], Study no. 4 [2019], Study no. 5 [2018]).

Study n°1: "Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes".

Study n°2: "Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco".

Study n°3 : "These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking".

Study n°4 : "Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014-2016 declined faster

Not referring to ACKNOWLEDGMENTS

There is no specific mentioning of harm reduction in the specific ToR (Section 2.1). The mentioning of harm reduction in the background is linked to cessation ("their role in harm reduction/cessation of traditional tobacco smoking" – so their role for reducing harm through cessation. There is no stand-alone harm reduction point in these ToR. Therefore the SCHEER Opinion focuses only on health impacts compared to non-smoking.

The Opinion was updated highlighting this position in Abstract, Summary, the Scientific Opinion (Section 3) and the Introduction of the Rationale (Section 6.1).

The substitution of ENDS for cigarette smoking as a viable strategy for improving individual and public health was not within the ToR.

Please see table 1, answer 6.

than predicted by the preceding trend, suggesting the absence of a substantial gateway effect".

Study n°5 : "While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping's ascendance".

lines 49 to 51: finally, this section indicates that there is little evidence that vapoter helps to stop smoking.

These conclusions contradict the results of several studies (Study No. 1 [2019], Study No. 2 [2017]), which have already shown that the use of an electronic cigarette increases the chances of quitting smoking.

Study 1 shows that "electronic cigarettes are more effective in stopping smoking than nicotine replacement therapy, when both products are accompanied by behavioural support". Study 2 notes in its conclusions that "almost everyone smoked before starting to vaporize. A large majority of them recognised that, unlike other smoking cessation aids, they could stop smoking through vaporising".

Study 1: "E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support". Study n°2: "Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping". Translated with www.DeepL.com/Translator (free version)

481	Colombo Massimilia no , Devatech S.r.l, Italy	ACKNOWLEDGMENTS	<p>Good Morning, In first time thank you very much for your attention. My Name is Massimiliano, I m graduated in Mechanical Engineering and is 8 years that I used the the electronic device . I stop of smoking cigarettes and when to start vaping my healthy condition is grow up. I think the vaping is the correct way to stop the smoking. I wish you have a nice day and in the case you have need for other information on clarification I remain at your disposal. Best regards Massimiliano</p>	Thank you for your comment.
482	No agreement	ACKNOWLEDGMENTS	I accuse this document of being unobjecive and not using all the scientific studys and evidences.	Thank you for your comment.

to disclose
personal
data

483	Paciaroni Roberto,luca svapo di roberto paciaroni, Italy	ACKNOWLEDGMENTS	<p>lines 13 and 14: this part indicates that the risks of cardiovascular problems due to vaping are high.</p> <p>However, this study, which aimed to compare the "potential risks of e-cigarette use, with the well-established devastating effects of smoking" explains in its findings that the currently available evidence indicates that "e-cigarettes are by far a less harmful alternative to smoking "and that" there are health benefits in smokers who switch from tobacco to electronic cigarettes".</p> <p>lines 42 to 44: these lines note that vaping is a gateway to smoking.</p> <p>However, a large number of scientific studies have already shown that no, vaping does not lead to smoking. (Study No. 1 [2020], Study No. 2 [2016], Study No. 3 [2014], Study No. 4 [2019], Study No. 5 [2018]).</p> <p>Study 1 concludes that "there is no evidence of an increased risk of switching to daily smoking at the age of 17 in smokers who have already smoked and who have also tried e-cigarettes".</p> <p>Study 2 indicates that "two thirds of exclusive e-cigarette users in the past 30 days have already consumed tobacco".</p> <p>The third explains that his data "does not suggest that e-cigarettes can facilitate smoking and suggests that it is quite widely used for smoking cessation."</p> <p>Work no. 4 indicates in its conclusions that "data from five surveys on young people in the United States and the United Kingdom show (...) the absence of a significant gateway effect".</p> <p>Finally, research no. 5 explains that "although trying electronic cigarettes can lead to an increase in smoking in some young people, the overall effect at the population level appears negligible given the reduction in smokers during the period of increased vaping".</p> <p>Original versions of the conclusions of the various studies:</p> <p>Study n ° 1: "Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also</p>	Please see the reply to comment 480.
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experimented with e-cigarettes”.

Study n ° 2: "Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco" ..

Study n ° 3: "These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking".

Study n ° 4: "Data from five surveys in US / UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect”.

Study no.5: "While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping's ascendance”.

lines 49 to 51: Finally, this part indicates that there is only weak evidence that vaping helps quit smoking.

These conclusions contradict the results of several studies (study no.1 [2019], study no.2 [2017]), which have already shown that the use of an electronic cigarette increases the chances of quitting smoking.

The study n. 1 shows that "e-cigarettes are more effective for smoking cessation than nicotine replacement therapy when both products are accompanied by behavioral support."

The study n. 2 notes in its findings that “almost everyone smoked before starting to vape. The vast majority of them recognized that, unlike other cessation aids, they could quit smoking through vaping ”.

484 No agreement to disclose personal data
ACKNOWLEDGMENTS

Line 42-43-44:
A large number of scientific studies have already shown that no, vaping does not lead to smoking. Vaping helps to quit smoking, there is no doubt about this!

Please see Table 1, answer 6.

485 Becher Rune,Norwegian Institute of Public
ACKNOWLEDGMENTS

The professional background of the members and the external experts behind the report appears excellent.

Thank you for your comment.

Health, Norway			
486 O'Leary Renee, Cen ter of Excellence for the Accelerati on of Harm Reduction, University of Catania, Italy, Italy	ACKNOWLEDG MENTS	The following members of the Center of Excellence for the Acceleration of Harm Reduction (CoEHAR) attest to the accuracy and veracity of the comments submitted as signatories. 1. Salvatore ALAIMO; 2. Carmelina Daniela ANFUSO; 3. Ignazio BARBAGALLO ; 4. Francesco BASILE; 5. Sebastiano BATTIATO; 6. Gaetano BERTINO ; 7. Alberto BIANCHI ; 8. Antonio G. BIONDI; 9. Maria Luisa BRANDI ; 10. Emma CACCIOLA ; 11. Rossella R. ACCIOLA ; 12. Bruno Santi CACOPARDO ; 13. Aldo E. CALOGERO ; 14. Maria Teresa CAMBRIA ; 15. Davide CAMPAGNA ; 16. Filippo CARACI ; 17. Agatino CARIOLA ; 18. Massimo CARUSO ; 19. Pasquale CAPONNETTO ; 20. Fabio CIBELLA ; 21. Maurizio DI MAURO ; 22. Santo DI NUOVO ; 23. Adriana DI STEFANO; 24. Filippo DRAGO; 25. Salvatore FAILLA; 26. Rosario FARACI; 27. Salvatore FERLITO; 28. Margherita FERRANTE; 29. Alfredo FERRO; 30. Giancarlo A. FERRO; 31. Francesco FRASCA; 32. Lucia FRITTTITA; 33. Pio M. FURNERI; 34. Antonio GAGLIANO; 35. Giovanni GALLO; 36. Fabio GALVANO; 37. Giuseppe GRASSO; 38. Francesca GUARINO ;39. Antonino GULINO ; 40. Emmanuele A. JANNINI ; 41. Sandro LA VIGNERA ;42. Giuseppe LAZZARINO ; 43. Giovanni LI VOLTI, Director ; 44. Antonio LONGO ; 45. Gabriella LUPO ; 46. Mario MALERBA ; 47. Luigi MARLETTA ; 48. Guido NICOLOSI ; 49. Francesco NOCERA ; 50. Renée O'LEARY ; 51. Gea OLIVERI CONTI ; 52. Rosalba PARENTI ; 53. Riccardo POLOSA, Founder; 54. Alfredo PULVIRENTI; 55. Francesco PURRELLO ; 56. Francesco RAPISARDA ; 57. Venerando RAPISARDA ; 58. Michele REIBALDI ; 59. Renata RIZZO ; 60. Simone RONSISSVALLE ; 61. Martino RUGGIERI ; 62. Maria C. SANTAGATI ; 63. Cristina SATRIANO ; 64. Laura SCIACCA ; 65. Maria Salvina SIGNORELLI ; 66. Marco TATULLO ; 67. Daniele TIBULLO ; 68. Venera TOMASELLI ; 69. Luca ZANOLI ; 70. Agata ZAPPALÀ	There is no comment in this contribution.
487 Comperno le Thomas, Br itish American Tobacco, B elgium	ACKNOWLEDG MENTS	BAT welcome the European Commission's efforts to understand the most recent scientific and technical information on e-cigarettes, as part of their review of the Tobacco Products Directive 2014/40/EU. However, we are disappointed with the Preliminary Opinion by SCHEER, which does not reflect the totality of the existing science on e-cigarettes. The SCHEER working group, supported by external experts, have omitted a significant body of literature on the role of e-cigarettes in providing public health benefits compared to continued cigarette smoking in an EU context. For example, the many peer-reviewed publications from industry scientists are noticeably absent.	There is no specific mentioning of harm reduction in the specific ToR (Section 2.1). The mentioning of harm reduction in the background is linked to cessation ("their role in harm reduction/cessation of traditional tobacco smoking" – so their role for reducing harm through cessation. There is no stand-alone harm reduction point in these ToR. Therefore the SCHEER Opinion focuses only on health impacts compared to non-smoking. The Opinion was updated highlighting this position in Abstract, Summary, the Scientific Opinion (Section 3) and the Introduction of the Rationale (Section 6.1). The substitution of ENDS for cigarette smoking as a viable strategy for improving individual and public health was not within the ToR.

We have therefore included our 53 peer-reviewed e-cigarettes publications including studies reporting on testing emissions, toxicological data, risk assessment of e-liquids flavours and ingredients, consumer and clinical studies and population modelling, for SCHEER's consideration. We have published our research in international peer-reviewed journals, choosing an open access option where possible, so there are no restrictions on who can read our research, and links to all of these articles can be found in the library of www.bat-science.com, our dedicated science website, along with our @BAT_Sci twitter handle.

We are open and transparent about the scientific research that we do, also developing scientific collaborations with a wide range of groups. We actively participate in technical working groups, sit on steering committees and advisory panels, and also present our studies at international conferences, ranging from chemistry and toxicology to more specialist events on nicotine and tobacco science or aerosol science.

We cordially invite the SCHEER working group, external experts and other members of the SCHEER committee to visit our R&D site in Southampton, UK to learn more about the research that we conduct on e-cigarettes and also meet with our product developers and compliance teams to understand how we ensure our products are compliant with EU regulations. Since 2011, when we first developed our science exhibition centre, we have welcomed over 3500 visitors, all of whom wanted to learn more about the science behind e-cigarettes and other products. The groups have been diverse, ranging from science writers, mainstream media, journalists, academics, scientific collaborators, public health representative, regulators as well as consumer advocates.

E-cigarettes have a critical role for public health, for millions of adult EU smokers, as alternatives to smoking. We strongly encourage SCHEER to consider the important public health principle of tobacco harm reduction and to reconsider the conclusions in the draft Preliminary Opinion, referring to the literature attached.

The SCHEER refers to the methodology section 4, explaining that a literature search was performed until April 2019. The search terms used are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019. In addition, the SCHEER made use of reports by other organizations on this topic, as well as on information provided by the Commission. literature provided in the public consultation was considered based on these criteria.

488	Olteanu Vlad, Juul Labs Inc. , Belgium	ANNEX 1: ANALYTICAL METHODS	It is unclear why Annex 1 was included when it was not referenced in the body of the Opinion.	An additional phrase has been included in the body of the Opinion.
489	Compernelle Thomas, British American Tobacco, Belgium	ANNEX 1: ANALYTICAL METHODS	<p>This Annex aims to provide the most appropriate methodology for the assessment of aerosol constituents in e-cigarettes. We respectfully request SCHEER to correct and amend the following:</p> <p>(P95, LN5): refers to cigarette smoke, should this state e-cigarettes aerosol? As both e-liquid and aerosol condensate are liquid many methods consist simply of dilution with a suitable solvent and analysis using a combination of chromatographic separation and spectroscopic detection</p> <p>(P95, LN14-17): no reference(s) provided.</p> <p>(P95, LN18-20): “The agreement” to what? This text doesn’t refer to methods for PG detection/quantification. Reference 6 is mentioned, but not listed in Table A.1.1. Please can this be clarified?</p> <p>(P95, L21-23) citations are inaccurate – only ref 10 included analysis of metals and these comprised only Ni, Pb and Cd, which were also detected in the Nicorette inhalator control. Ref 10 seems popular with the authors of the report – they re-cite it as ref 15 and ref 39. It is also cited in other sections as a source of emissions data but the data are not necessarily representative of current products – see final comment and table below.</p> <p>(P95, L32-37): seems to classify carbonyls as nicotine degradation products, which is incorrect. As noted by the authors, vaping conditions affect carbonyl emissions significantly and, by their own admission (P35, L10) “Studies with controlled realistic (puffing) conditions are rare”, suggesting that the majority of carbonyls emissions data are not relevant for the assessment of consumer exposure.</p> <p>(P95, L44) title of Table A.1.1 states “methods for nicotine and nicotine-related compounds”, however, the inclusion of a column for metals for example does not fit with the title.</p> <p>(P97, L9) Table A.1.3, entry for “Heavy metals” under “Electronic cigarette liquid” lists Sn, Cu and Ni in the column providing instrument techniques</p> <p>Considering the references from which the majority of emissions data are drawn (see list below), they were published between 2012 and 2014 and assessed only early generation e-cigarettes, typically disposables (15, 23)</p>	<p>Thank you for your suggestions.</p> <p>The text has been amended.</p> <p>The reference(s) has been added.</p> <p>The text has been partially rephrased. Ref.6 is mentioned in the body text.</p> <p>The references have been replaced with more recent ones.</p> <p>No changes needed.</p> <p>It has been rephrased.</p> <p>A comma has been included, separating heavy metals from the others metals.</p> <p>No changes needed.</p>

or early replacement liquids (17). These results may not be representative of the current generation of cartomizers and should be replaced or augmented by more current data:

Ref #15: Goniewicz et al 2014 (Approach: 10 cartridge + 2 cartomizer ecigs vs Nicorette; single port puff machine) - Devices were 150 puff equivalent cigalikes. Authors detected Ni, Pb, Cd, FA, AA in the Nicorette emission, suggesting a chemical background issue.

Ref #17: Kim et al 2013 (Approach: HPLC/MS/MS of 105 e-liquids from 11 manufacturers in Korea) - SPE and liquid partition. Total TSNAs 13±18ng/mL. NNN relatively high, proposed to be formed in e-liquid.

Ref #19: Lim & Shi 2013 (Approach: unable to find full manuscript online; cited by others) - Headspace GC/MS of aldehydes in liquids seems unlikely to measure carbonyl emissions accurately.

Ref #21: Schripp 2013 (Approach: abstract only) - 8m3 room is 'close to real use'? Particle count and VOCs.

Ref #23: Williams et al 2013 (Approach: dissected 22 samples of a single cartomizer product) - Range of spectroscopic and imaging methods. Data are for early ecig. Later Williams papers also focus on disposable ecigs.

Ref #24: McAuley 2012 (Approach: Compared vapour of 4 ecig products to cigarette smoke in room air) - Vapour emissions (carbonyls, VOCs, PAHs, TSNAs) gave 'no significant risk' of cancer.

We would kindly refer SCHEER to the literature attached providing more recent and appropriate methodology for the assessment of aerosol constituents in e-cigarettes.



Annex_1_References.pdf

See Table 1, answer 11. Some references have been replaced and adapted.

490 Compernelle Thomas, British American Tobacco, Belgium
ANNEX 2: INGREDIENTS IN E-LIQUIDS

Since this Annex is intended to supplement Section 6.4, this needs to present the most up to date and relevant information regarding ingredients in use in EU e-liquids. The SCHEER review should focus on the ingredients and any associated risks, reported here, as opposed to scientific papers reporting on ingredients found in e-liquids from outside the EU or from before the introduction of the TPD in the EU. This is misleading and also does not represent the totality of the current e-liquid offerings in the EU.

See Table 1, answer 1.

E.g., (P30, LN24-25) Ethylene glycol should be deleted as a solvent

No changes needed.

carrier in e-liquids because Annex 2 demonstrates it is irrelevant to current e-liquids within the EU (the original mention was presumably based on Hutzler et al 2014, which found it in pre-TPD German e-liquids).

Similarly, (P30, LN34; P30, LN37; P36, LN12-19; P55, L47) refer to reports of diacetyl being highly prevalent in e-liquids, referring to early US and pre-TPD reports, whereas this Annex shows no diacetyl in use in current EU e-liquids, so mentions of diacetyl-associated issues can be deleted throughout the SCHEER report.

No changes needed.

Also, based on this information, all sections suggesting issues with TSNAs and tobacco alkaloids need to be reviewed in the report, whether this concerns risks to the main user or bystander risks. This list indicates tobacco extracts or oils are not used, so the only possible source of those compounds would be from impurities in the nicotine. Within the EU, TPD requires the ingredients used to be of high purity and various national standards (1,2) clarify that for nicotine, this means using pharmaceutical grade purity. So any concern around TSNAs and tobacco alkaloids from e-liquids is very low, and comparable to that from nicotine replacement products.

See table 1, answer 4.

We therefore request that SCHEER ensure that information presented in the Annex and related chapters refer to the current status of e-liquid ingredients as per current regulations stipulated as part of TPD.

See Table 1, answers 1 and 4.

Ref:

British Standards Institute. Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly-related products. Manufacture, importation, testing and labelling. Guide. London: BSI; 2015. Ref. No. PAS 54115:2015.

Association Française de Normalisation. Electronic cigarettes and e-liquids – part 2: requirements and test methods for e-liquids. Paris: AFNOR; 2015. Ref. No. NF XP D90-300-2:2015.

491	Olteanu Vlad, Juul Labs Inc., Belgium	ANNEX 2: INGREDIENTS IN E-LIQUIDS	Annex 2 is referenced three times in the body of the opinion: Page 23, lines 33-35, “The Opinion makes use of information from competent authorities in the Netherlands and Greece, which have compiled lists of most common ingredients of e-liquids (see tables
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No changes needed.

			in Annex 2).” Page 25, line 1-2, “Data based on information from the Netherlands (NL) supported by data from Greece (GR). More information, e.g. on maximum values are given in Annex 2.” Page 55, lines 43-45, “It is noted that the composition of the aerosols as measured only match with the lists of top ingredients in liquids as presented in Annex 2 (present in > 10% liquids) for nicotine, carrier liquids, ethyl acetate and ethanol.”	
			No reference is provided for where the Committee got this information making it impossible to assess, e.g., the “competent authorities” are not cited.	Out of scope of the opinion.
492	Olteanu Vlad, Juul Labs Inc., Belgium	ANNEX 3: OVERVIEW PUFFING PARAMETERS AND TESTING CONDITIONS	Annex 3 provides overview tables of puffing parameters and testing conditions from studies reviewed in DeVito and Krishnan-Sarin, 2018 and Evans and Hoffman, 2014. Where Annex 3 is referenced (Page 27, lines 1-31) it is noted that only some of the original studies provided in these reviews were included. “The four studies (Strasser et al., 2016; Behar, et al., 2015; Norton et al., 2014; Farsalinos et al., 2015) reviewed in DeVito and Krishnan-Sarin, 2018 are summarised in table A3.1 in Annex 3.,” and “The four studies (Etter and Bullen, 2011; Hua et al., 2013; Farsalinos et al., 2013; Trtchounian et al., 2010) reviewed in Evans and Hoffman, 2014 are also summarised in table A3.1 in Annex 3” This is out of a total of at least 29 combined studies from both reviews. There is no justification provided for why only these 8 studies were included in the Opinion.	See Table 1, answer 11.
493	Compernelle Thomas, British American Tobacco, Belgium	ANNEX 4: LITERATURE – SEARCH TERMS USED	SCHEER’s selective evidence fails to meet the required standards of scientific advice set out in its Rules of Procedure, including the requirements of transparency and consideration of the best, and the most recent scientific and technical information available. The search strategy applied in the Opinion is not transparent and thus is not reproducible. Specifically, details on the databases used for the search, including Boolean search terms, were not provided. There is no list of excluded studies, nor are there details to identify a clear methodology for study inclusion or selection in the evidence synthesis.	AFNOR XP D90-300-3 standard and related standards have been added to this opinion. No changes needed.
			The search strategy is not objective. The Opinion lacks a methodologically sound approach for study selection from the literature search results. Furthermore, without a justification for the	See Table 1, answer 11.

			<p>identified search timeframe, the methodology could potentially lead to the unintended exclusion of important studies on specific topics that were published outside of a subjective timeframe. Finally, there is no method provided for the decision to include studies outside of the search timeframe. What is evident, the most recent and best available scientific studies were not selected to help inform an objective evaluation on the relative health risks of e-cigarettes compared to cigarettes.</p> <p>The search strategy is not comprehensive. Presentation of Annex 4 and the overall number of studies indicates that a combined search was conducted for all outcomes investigated. Hence, search results may have been inadequate because search terms could interact with each other, excluding studies that may have been identified if an outcome-specific search had been conducted.</p> <p>In conclusion, the Opinion should have followed a transparent, reproducible, comprehensive, and objective search strategy, as outlined in systematic review methodology guides (1,2). Ref: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester (UK): John Wiley & Sons; 2019. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;6(7):e1000100.</p>	<p>No changes needed.</p> <p>See Table 1, answer no.3.</p>
494	Olteanu Vlad,Juul Labs Inc. ,Belgium	ANNEX 4: LITERATURE – SEARCH TERMS USED	<p>Annex 4 is referenced on page 19, lines 24-25 “To address the terms of reference of this Opinion, the Commission library service performed a literature search until April 2019. The search terms used are listed in Annex 4.” We notice that the request from the Commission states that the types of documents to be used include, peer reviewed articles, journal entries, book chapters, government and non-government funded publications. Notably absent from this request is the use of primary sources of research which would increase the quality of this Opinion.</p> <p>Please see file attached.</p>  <p>List_of_abbreviations.pdf</p>	See Table 1, answer no.11.
495	No agreement to disclose personal data	LIST OF ABBREVIATIONS	<p>Please see file attached.</p>  <p>List_of_abbreviations.pdf</p>	No changes needed.

496	Poirson Philippe, Sovape, France	MANDATE FROM THE EU COMMISSION SERVICES	<p>[p.9 l. 7-9] We point out that TPD has created completely different conditions than in the United States. As shown by the ITC 4 countries (Hua-Hie Yong, 2017), regulatory conditions strongly influence the behaviour of vaping users. These points should be borne in mind by readers in their assessment of this report, especially the evidence from studies on the US situation.</p> <p>Also SCHEER precise evaluating only nicotine vaping, as covered by the TPD. Therefore, population data mixing uses of nicotine-free and nicotine vaping indiscriminately, such as US data, should not be used. Finally, the TPD has created rules for authorising vaping products, so analyses of products that do not meet these rules should be presented as such, or excluded for lack of relevance.</p>	Please see Table 1, answer 8.
497	No agreement to disclose personal data	MANDATE FROM THE EU COMMISSION SERVICES	<p>IMPERIAL BRANDS (IMB) BELIEVES THE OPINION FAILS TO RESPECT OR ONLY PARTIALLY RESPECTS THE MANDATE RECEIVED FROM THE EU COMMISSION</p> <p>Page 9 Line 12: ‘Further, the Commission shall be assisted by ‘scientific and technical experts in order to have all the necessary information at its disposal’; the SCHEER Opinion only takes into account a selected and limited number of scientific studies and evidence over a limited period of time (from January 2015 to April 2019), failing to take into consideration studies and findings before 2015 and those which have emerged over the last 18 months.</p> <p>P9 L15: On this basis, any further proposals over the ‘elements of the Directive which should be reviewed or adapted in light of scientific and technical developments’ would only have a partial and limited scientific and technical grounding.</p> <p>When addressing the EP ENVI Committee, Commissioner Kyriakides clearly stated she is a firm believer in basing policy decisions on science and agreed there was a considerable problem with disinformation in the EU.</p> <p>If the review of Art. 20 of EUTPD was based solely on SCHEER’s Opinion, it could not claim to be based on the entire scientific evidence available, thus contributing to the disinformation around e-cigarettes.</p>	<p>The SCHEER refers to the methodology section 4, explaining that a literature search was performed until April 2019. The search terms used are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019. In addition, the SCHEER made use of reports by other organizations on this topic, as well as on information provided by the Commission.</p> <p>Additional literature provided in the public consultation was considered based on these criteria.</p>

498	Olteanu Vlad, Juul Labs Inc., Belgium	MANDATE FROM THE EU COMMISSION SERVICES	2 Mandate from the EU Commission Services and 2.1 Terms of Reference	<p>At several points in the report and literally on page 20, lines 26-27 of part 6.1 (Introduction) of the Opinion, SCHEER notes that “this Opinion is restricted to the terms of references given by the European Commission”. It is therefore important to understand both the letter and the intention of those terms of reference. The terms of reference clearly state that “the main purpose of the scientific opinion is to assist the Commission in assessing the most recent scientific and technical information on e-cigarettes.” (page 10, lines 3-4) This assessment is part of and will feed into the report that the TPD requires out of the Commission services by 21 May 2021.</p> <p>Lines 4 to 8 of the Mandate (page 9) establishes that both the Commission report and the scientific review performed by SCHEER comes directly from the co-legislators volition expressed within TPD, which is described as “aim(ing) to improve the functioning of the internal market for tobacco and related products, while ensuring a high level of health protection for European citizens.” It is also noted that Article 20 of the Tobacco Products Directive “introduces for the first time a comprehensive regulatory framework for electronic cigarettes with a focus on safety, quality, consumer protection and collection of information.” A joint reading of those two parts should indicate that:</p> <ul style="list-style-type: none"> -Only e-cigarette products available to EU consumers within the internal market and regulated by TPD should have been considered by SCHEER in a review of TPD rules on e-cigarettes. These are products marketed within the EU after 20 May 2016 and/or those marketed in EU Member States from the date of their TPD transposition (between 21 May 2014 and 20 May 2016). The use of TPD compliant e-cigarettes are the most relevant to the safety of the EU citizens and their quality and level of consumer protection should have been the main focus of the SCHEER review. -Data and studies collected/performed by Member States regulatory authorities reviewing TPD-compliant electronic cigarettes marketed on their territories were not reviewed by SCHEER (including the Public Health England Study 2020 uploaded under
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The SCHEER refers to the methodology section 4, explaining that a literature search was performed until April 2019. The search terms used are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019. In addition, the SCHEER made use of reports by other organizations on this topic, as well as on information provided by the Commission.

Additional literature provided in the public consultation was considered based on these criteria.

this heading). Such data and studies, collected and released by independent, reputable and well-respected national regulatory authorities should have been thoroughly reviewed and used to the full extent.

-The e-cigarette industry is highly innovative, which means that product design and characteristics rapidly evolve. Scientific reviews of both product design and characteristics (including those relating to nicotine delivery) therefore appear in rapid succession. Only the most recently available scientific and technical information should have been included here, including, as mentioned, scientific and technical studies performed on EU marketed devices and liquids after 2014. Comparison of pre and post TPD enforcement characteristics (studies dating before 2014 but assessing EU marketed devices and liquids) could also have been performed.

-Reviews from other markets (including United States) could have been used as comparison points (for instance where nicotine content in mg/ml has a significant variance) to EU marketed products.

-Given the general purpose of TPD but also considering the well documented consumer substitution of combustible tobacco for e-cigarette products, a proper understanding of any potential human health effects of e-cigarettes would have included a proper assessment of not just absolute but risk relative to combustible cigarettes, which e-cigarettes are designed to replace.

Ref:

McNeill (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020. A report commissioned by Public Health England
 GOV.UK. (2018). Press release. PHE publishes independent expert e-cigarettes evidence review

499	Michel Nicolas, Association Romande des Professionnels de la Vape, Switzerland	MANDATE FROM THE EU COMMISSION SERVICES	<p>2. MANDATE FROM THE EU COMMISSION SERVICES</p> <p>Page 9</p> <p>22 Open questions</p> <p>23 particularly include the role of e-cigarettes in relation to their use and adverse health effects</p> <p>24 (i.e.; short- and long-term effects), their role as a gateway to smoking / the initiation of</p> <p>25 smoking (particularly focusing on young people), their role in harm reduction / cessation of</p> <p>26 traditional tobacco smoking, as well as risks associated with</p>	<p>There is no specific mentioning of harm reduction in the specific ToR (Section 2.1). The mentioning of harm reduction in the background is linked to cessation (“their role in harm reduction/cessation of traditional tobacco smoking” – so their role for reducing harm through cessation. There is no stand-alone harm reduction point in these ToR. Therefore the SCHEER Opinion focuses only on health impacts compared to non-smoking.</p> <p>The Opinion was updated highlighting this position in Abstract, Summary, the Scientific Opinion (Section 3) and the Introduction of the Rationale (Section 6.1).</p>
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			<p>their chemical composition (e.g.; number and levels of toxicants). The mandate of the commission includes a comparison of the risks between vape and tobacco, since it requires on the one hand a study of the toxicity of the vape, on the other hand an analysis of its potential as a reduced risk product. In other words, the SCHEER report should include an analysis of the benefit / risk balance. This balance seam useful in order to allow EU commission to take a decision based on science.</p> <p>The SCHEER report was requested by the EU commission to provide decision-making elements. Defining the strength of the current evidence is in itself necessary but insufficient. The SCHEER report should also quantify the risks, in particular by comparing them with other products known and emitting a similar toxicity: Burned, heated tobacco, snus, NTRs or even a candle (aldehydes), a tomato (heavy metals) or an eggplant (nicotine). When standards or recommendations regarding exposure to toxic components are available, the SCHEER report should cite them and indicate whether existing studies indicate that the toxic emissions from the vape are below or above the standards.</p>	<p>The substitution of ENDS for cigarette smoking as a viable strategy for improving individual and public health was not within the ToR.</p>
500	<p>Saunders Emily,Broughton Nicotine Services,United Kingdom</p>	<p>MANDATE FROM THE EU COMMISSION SERVICES</p>	<p>Page 9, lines 1-50 There is significant variation in adaptation of the TPD across the member states, especially around emissions testing and ingredient reporting. When it comes to something like emissions testing, there's no possible way that products can be compared, e.g. specific components that must be measured, but even something as simple as no harmonisation on reporting units which would be helpful across the board.</p>	<p>Thank you for your comment.</p>
501	<p>Landl Michael,World Vapers' Alliance,Austria</p>	<p>METHODOLOGY</p>	<p>Page 20, Lines 24 - 42: Regarding the articles that the Committee chose in order to prepare this preliminary opinion have missed a number of opportunities in terms of telling the full story on vaping. Notably, no mention whatsoever has been made about anecdotal evidence from millions of smokers who have quit due to vaping. CASAA (the North American Association advocating for smoke-free alternatives) has over 10.000 testimonials on their website from people who have quit smoking by vaping.</p> <p>Beyond just anecdotal evidence, there are a number of studies which make this point very clear, which, once again, were not taken</p>	<p>Please see Table 1, answer 2.</p>

into consideration by the SCHEER Committee. These include one study [1], which concludes that “E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy”, and another group of scientists [2], which conclude that “The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level.”

Moreover, a recent Cochrane Systematic Review [3] of more than 50 studies and more than 12,000 participants, found that e-cigarettes with nicotine can help more people to quit smoking than traditional nicotine replacement therapy (such as gums or patches) or e-cigarettes without nicotine.

References:

- [1] Jackson, S. E., Kotz, D., West, R., and Brown, J. (2019) Moderators of real-world effectiveness of smoking cessation aids: a population study. *Addiction*, 114: 1627–1638.
- [2] - Zhu Shu-Hong, Zhuang Yue-Lin, Wong Shiushing, Cummins Sharon E, Tedeschi Gary J. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys *BMJ* 2017;
- [3]- Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, Notley C, Rigotti NA, Turner T, Butler AR, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database of Systematic Reviews* 2020, Issue 10. Art. No.: CD010216.

Please see Table 1, answer 6.

502 Serpytis
Pranas, Vilnius
University
Medical
Faculty
Clinic of
cardiology,
Lithuania

METHODOLOGY

Page 19. The data provided represents US situation although the document is intended for EU use. Regulations, practices and products used in the US and EU differ often therefore cannot be extrapolated automatically so conclusions are rather biased and not reflecting the actual situation in the EU, Further research and EU data collection is needed to create solid basis of EU evidence.

Please see Table 1, answer 8.

503 Poirson
Philippe, Sovape,
France

METHODOLOGY

[p. 19 l. 33-42] SCHEER acknowledges that US products do not meet EU requirements. The acknowledgement should not relieve SCHEER from assessing the relevance for each case of the results in relation to the actual situation in Europe. This passage reflects a lack of rigour in the criteria of the review work by SCHEER.

Please see Table 1, answer 8.

504 Pietsch
Franz, Austria

METHODOLOGY

When assessing the health risk from e-cigarettes, the potential for dependence on nicotine is not taken into account. It is not clear why the

Please see Table 1, answer 6.

rian
Federal
Ministry of
Social,
Health,
Care and
Consumer
Protection,
Austria

SCHEER report disproportionately assesses the gateway effect compared to the effectiveness of e-cigarettes in quitting smoking. The question arises why the SCHEER report only deals with the help of e-cigarettes as an aid to smoking cessation or quitting smoking in an abbreviated way. The SCHEER report, launched in September 2020, couldn't take into account the Cochrane review published in October 2020 on the effectiveness of e-cigarettes as an aid in smoking cessation (<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full>).

The elucidations in the "Preliminary Opinion on electronic cigarettes" of the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) are in general considered to be of high value. However, some recently very important issues regarding health risks of e-cigarettes have not been addressed. The scientific substantiation of these issues would be of great value to enable regulatory measures. Furthermore, the description of the conducted risk assessments is lacking adequate transparency.

In the opinion it is stated that e-liquids mainly comprise of propylene glycol, glycerol, nicotine, water, flavourings and preservatives. However, there is no common definition of an "e-liquid" regarding its ingredients available (e.g. in the Directive 2014/40/EU). In fact, there are products available, which contain e.g. a considerable amount of oils (MCT) as main carrier. Health risks of e-liquids containing oil are not well known so far. However knowledge about health risks associated with the aspiration of oils are well known and appear to be incomparably higher than those associated with propylene glycol or glycerol.

We believe that such issues, which involve major health hazards should be included in an opinion on electronic cigarettes. A scientific substantiation is highly required to enable regulatory measures (e.g. a more precise definition of e-liquids regarding the ingredients) to facilitate adequate consumer protection.

Furthermore, contaminants have not been considered in the opinion. However, we are of the opinion that contaminants should be added, as they could potentially pose health risks. The current legislation does not enable to take measures, as article 20 (3) e only refers to ingredients and does not cover contaminants. A data collection of contaminants in e-liquids and an evaluation of associated risks would be of high value. A scientific substantiation of potential risks of contaminants is highly required to enable regulatory measures to facilitate adequate consumer protection.

The description of the conducted risk assessment is not transparent. The

Please see Table 1, answer 2.

Contaminants are mentioned in the Opinion, whenever they appear in the literature, i.e. metals.

ultimately important information is not given. A detailed list of applied points of departure for each substance and according elucidations, which MOE would be sufficient to reach a conclusion of low concern (as it is described on page 56, lines 33-46) is not given. This information is needed to form an objective independent expert's opinion on the methodological soundness of the applied procedure. In addition, the lack of this information prevents the reproduction of the risk assessment, which would be of great value for regulatory controls.

Please see Table 1, answer 3.

It is not clear whether the risk assessments results are calculated separately for this opinion, or whether they are taken from the previous study (Visser et al. 2014). This original study might include the lacking information regarding PoDs and MOEs, yet it is not available in English. An English translation (Visser et al. 2015) of this study represents only a short version and does not include PoDs and MOE assessments.

Please see Table 1, answer 2.

505 Becher
Rune,Norwegian
Institute of
Public
Health,Norway

METHODOLOGY

We encourage inclusion of more information regarding the methods used, this because we are concerned about the lack of a detail in description of the method used as a basis for the electronic searches and the assessment of the quality of the included studies. Search strategies are not stated (keywords only), therefore it is not possible to assess or reproduce the search.

Please see Table 1, answer 2.

The inclusion or exclusion criteria are not described, making it difficult to judge whether they have been followed. It is also unclear how many people screened and selected references, and it is unclear how the selection was made; if there were two or more review articles on the same topic.

How was studies associated with or financed by the tobacco industry treated? It seems that the report to some extent includes studies where some of the authors are or have been funded by the tobacco industry. To what extent this is the case, should be documented.

Source of funding is mentioned in the Opinion where appropriate.

506 No
agreement
to disclose
personal
data

METHODOLOGY

Page 19 Line 35: THE EUTPD LIMIT ON E-LIQUID NICOTINE CONCENTRATION IS HINDERING ADULT SMOKERS TRANSITIONING AWAY FROM COMBUSTIBLE TOBACCO DUE TO SUBOPTIMAL NICOTINE SATISFACTION

Please see Table 1, answer 9.

The EUTPD mandates the maximum nicotine content of an e-liquid cannot exceed 20 mg/mL, which is a non-evidence based arbitrary

value. Post-EUTPD, research has shown that e-cigarette users using low nicotine level e-liquids may actually puff on their product more intensely and may be exposed to higher levels of carbonyls compounds. In this study, the authors' note that the cap on nicotine concentration at 20 mg/mL, set by the EUTPD, may therefore have the "unintended consequence of encouraging use of lower nicotine concentration e-liquid, in turn increasing exposure to carbonyl compounds through compensatory puffing"[1]. Moreover, both Public Health England and the UK Royal College of Physicians have stated the nicotine concentration limit imposed by the EUTPD is limiting the effectiveness of e-cigarettes as a smoking substitute, particularly amongst heavier smokers[2]. SCHEER fails to highlight these unintended consequences of the EUTPD maximum nicotine content in its Opinion.



Methodology.pdf

507	Chaplia Maria, Consumer Choice Center, United States	METHODOLOGY	Page 20, Lines 24 - 42:	Please see Table 1, answer 6.
<p>In order to develop a coherent vaping framework, it is not enough to look at one side of the coin. As was mentioned, there's overwhelming scientific evidence proving that [1] "E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy", and [2], that "The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level." Moreover, a recent Cochrane Systematic Review of more than 50 studies and more than 12,000 participants, found that e-cigarettes with nicotine can help more people to quit smoking than traditional nicotine replacement therapy (such as gums or patches) or e-cigarettes without nicotine.</p>				
508	Wyszynska-Szulc Agnieszka, Philip Morris Products	METHODOLOGY	P. 19 l. 28	The text has been amended.
<p>This section specifies the cut-off period for collecting and taking into account of articles for the period 01.01.2015 to April 2019. We would like to highlight that early studies (e.g. 2015, 2016) might be based on old generation e-cigarette devices and may not represent the current products on the market. The SCHEER's Opinion acknowledges the existence of four generations of e-cigarettes (p.</p>				

S.A.,Switz
erland

21 1.1). For this reason, we suggest to explicitly add a sentence declaring this “device generation issue” in the paragraph. The mentioned above cut-off date of April 2019 does not correspond with what is specified in annex 4 p.117 1.53 (i.e. no restrictions on the search period). We would also like to raise that a cut-off date which is older than one year (April 2019) neglects many recent publications and developments which are important and specific for EU countries, and which we reference in our responses to this consultation.

Please see Table 1, answer 2.

P. 19 l. 39-41
The use of data from outside EU (especially the U.S.) is abundant. Although understandable, due to their abundance, the reliance on data coming from the US is - in some sections (e.g. 6.5.1) - disproportionate, and in our opinion misleading. As highlighted by some experts (McNeill 2019), “Australia, by prohibiting the sale of nicotine e-cigarettes, and the United States, by currently having no regulatory standards and few marketing restrictions, are more appropriately labeled outliers.”

Please see Table 1, answer 8.

509 Serafimov Lubomir,Bulgarian Vape Association of Manufacturers, Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E-liquid, Bulgaria
METHODOLOGY
Page 19 lines 28-29, 33

The SCHEER Opinion specifies that it had used publications published until April 2019. After this date until the opinion was finalized and the public consultation was open there is a time span of an year and a half and despite the fact that SCHEER was supposed to provide assessment of “the most recent scientific and technical information on electronic cigarettes.” the Opinion leaves behind more than one year of relevant publications. Moreover, many of the scientific documents and publications used by SCHEER reflect the US market situation, while drawing untenable conclusions for the EU.

Please see Table 1, answers 2 and 8.

			<p>differences were observed when using machines generate emissions using the same protocol (Talih et al, 2020). For example, users of JUUL UK devices may adjust their puffing patterns to obtain similar levels of nicotine as obtained with the JUUL USA devices. It has been reported that when given low nicotine concentration liquids, electronic cigarette users increased puff frequency, duration and liquid consumption (Dawkins et al.2016), and the more intensive puffing regimen associated with the reduced nicotine liquids resulted in higher measured carbonyl emissions (Kosmider et al., 2017). This factor and the results from the study of Talih et al, would, therefore, suggest that to the extent that users seek a given nicotine dose, exclusive users of JUUL devices may be exposed to three times the CC and ROS emissions when using JUUL UK relative to JUUL USA.</p> <p>Talih, S., Salman, R., El-Hage, R. et al. A comparison of the electrical characteristics, liquid composition, and toxicant emissions of JUUL USA and JUUL UK e-cigarettes. <i>Sci Rep</i> 10, 7322 (2020). https://doi.org/10.1038/s41598-020-64414-5</p> <p>Dawkins, L. E., Kimber, C. F., Doig, M., Feyerabend, C. & Corcoran, O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. <i>Psychopharmacology (Berl.)</i> 233, 2933–2941, https://doi.org/10.1007/s00213-016-4338-2 (2016).</p> <p>Kosmider, L., Kimber, C. F., Kurek, J., Corcoran, O. & Dawkins, L. E. Compensatory Puffing With Lower Nicotine Concentration E-liquids Increases Carbonyl Exposure in E-cigarette Aerosols. <i>Nicotine Tob Res</i>, https://doi.org/10.1093/ntr/ntx162 (2017).</p>	<p>Please see Table 1, answer 8.</p>
512	No agreement to disclose personal data	METHODOLOGY	<p>Page 19 lines 28-29, 33-42</p> <p>The SCHEER’s report draws rather extensively from sources relevant to the situation in the United States. However, owing to the EU Directive no. 2014/40/EU (TPD), the EU regulatory framework is vastly different. This is primarily due to the facts that there has been a set of very concrete rules and regulations put in place, which also prevented an outbreak of the EVOLI crisis. In order to truly assess the situation within the EU we recommend using sources more relevant to situation in the member states.</p>	<p>Please see Table 1, answer 8.</p>
513	Olteanu Vlad,Juul Labs Inc. ,Belgium	METHODOLOGY	<p>Page 19, Lines 17-31: There are several issues regarding the methodology used to synthesize this report. The report references a previous memorandum (SCHEER 2018) on the weighting of evidence (WOE) but, it is not clear how this process was implemented here.</p> <p>WOE refers to an approach that uses a combination of information from several independent sources giving sufficient evidence to fulfill an information requirement - information from a single piece of evidence alone is rarely sufficient.</p> <p>The scientific assessments that should be carried out are described in this report but the methods used are not. Missing elements in the described</p>	<p>Please see Table 1, answer 2.</p> <p>The SCHEER disagrees with the comment.</p> <p>The methodology described in the PHE report is very close to the one used by the SCHEER.</p> <p>The readers of the Opinion should be aware of the approach described in the Opinion and the SCHEER’s “Memorandum on weight of evidence and uncertainties - Revision 2018”, which is publicly available (https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_014.pdf).</p>

methodology include the search terms and databases used to gather relevant literature, inclusion criteria, quality assessment and justification for inclusion of articles. The report simply states that most information is derived from review articles and that primary sources are used 'if necessary'.

This lack of transparency is in stark contrast to scientific reports by both Public Health England and the National Academies of Sciences Engineering and Medicine which include ten and nine pages dedicated to methodology, respectively. These reports listed databases, search terms, individual assessment criteria, inclusion criteria, methodology for evidence synthesis and definitions with regard to level of evidence assessments, all of which is notably missing from the present report. The inadequate reporting of methodology here means that readers need to be expert in the relevant topics in order to gain full understanding of the opinion provided by the committee and ensure accuracy.

Furthermore, the lack of clear methodology likely affected the references used by the committee and the resulting conclusions. For example, the report concludes that "the overall weight of evidence for risk for systemic cardiovascular effects in second-hand exposed persons due to exposure to nicotine is weak to moderate." (Page 2; line 33-25) While no definition is provided by the committee for "weak" or "moderate," the use of the word moderate does suggest that the WOE is significant.

Many of the references used to come to this conclusion in section 6.5.4 (pages 51-52) actually refer to second-hand exposure resulting from combustible cigarettes or suggest a hypothetical link of second-hand exposure to e-cigarettes based on evidence from combustible cigarettes without regard to the differences between combustible cigarettes and e-cigarettes.

We suggest that a more detailed methodology similar to those provided by NASEM, 2018 and PHE, 2018 would be appropriate. Where feasible, we suggest that the committee refer to the primary sources provided by the cited reviews to support their conclusions.

Martin and colleagues (2018) provide a more detailed framework for WOE than is outlined in the SCHEER 2018 memorandum. This framework included one detailed stage which is not mentioned in the 2018 memorandum -developing a detailed assessment protocol that is not fully described in either the 2018 memorandum or this SCHEER report.

The careful reader of the memorandum would recognize what 'weak' and 'moderate' evidence stands for.

The aim of this stage is not only to increase transparency in the focus and methodology selected for the assessment; but, also to determine and document the appropriate focus of the data, the questions to be asked and, perhaps most importantly, document the protocol for WOE assessment. Explicit reference to this stage of assessment planning would be helpful in the report to gain context and understanding of the objectives for this report.

Ref:

Martin (2018). Weight of Evidence for Hazard Identification: A Critical Review of the Literature. *Environ Health Perspect.* 2018 Jul 17;126(7):076001. doi: 10.1289/EHP3067. eCollection 2018 Jul.

McNeill A, Brose LS, Calder, R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England. 2018

Public health consequences of e-cigarettes, US National Academy of Science, Engineering and Medicine, January 2018
<https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes>

514 Compernelle
 Thomas, British
 American
 Tobacco, Belgium

METHODOLOGY

The weight of evidence (WOE) approach applied in the Opinion has several methodological limitations that undermine the transparency, reproducibility, comprehensiveness, and objectivity of this evidence synthesis.

Validity, an indicator of the extent to which a measurement process measures what it purports to measure, and reliability, the extent to which a measurement process yields the same results repeatedly, are critical considerations in an evidence synthesis (1,2), and the individual studies being interpreted. SCHEER's own WOE memorandum (2018) clearly states "For each line of evidence, the criteria of validity, reliability and relevance need to be applied and the overall quality has to be assessed" ((3) at P.4). However, without providing adequate and clear definitions or criteria, the Opinion's evidence synthesis is not transparent, not reproducible, potentially biased, and thus not generalizable.

The Opinion included outcomes that were not pre-defined in the Terms of Reference, e.g., reduction (Section 6.7). Furthermore, the Opinion did not disclose how specific outcome measures were identified, grouped, or discussed, which is problematic when certain pieces of evidence are collectively considered despite differing in outcome measures. For example, cessation studies were collectively presented despite heterogeneity among the comparators and abstinence duration (4). Consequently, the

The list of references have been published.

Please see Table 1, answer 2.

evidence synthesis is not objective, not comprehensive, and thus not generalizable.

The Opinion did not provide details on specific methods, measurements, and limitations that contributed to the upgrading or downgrading of the evidence. SCHEER's WOE memorandum (2018) suggests the use of other grading systems for quality of evidence assessment, including the GRADE approach (5). GRADE accounts for the risk of bias that can influence the estimate of effect, imprecision, and indirectness in study execution, application of results, and inconsistency and publication bias (3,5). The Opinion did not disclose details of its GRADE assessment, potentially rendering its quality of evidence conclusions unreliable and subjective. The application of an additional grading system would have strengthened this Opinion with transparency, reproducibility, reliability, and validity.

The Opinion's treatment and interpretations of systematic reviews are also inconsistent. Specifically, the Opinion reviewed several systematic reviews in Section 6.6, but there is no reference to a GRADE approach for the quality of evidence assessment. In Section 6.7, the Opinion specifies a GRADE rating for two systematic reviews; additionally, PRISMA guidelines (6) and AMSTAR 2 (7) would have rated the methodological and reporting quality of the reviews (8). This approach should have been applied throughout this evidence synthesis.

Finally, the methodological approach of the Opinion lacked a transparent, pre-defined analytic plan, critical study details (e.g., the number of studies from the search, the number of included studies), and study inclusion/exclusion criteria. The approach also lacked a clearly defined process for generating themes and how other methods (e.g., search strategy, analysis plan, how evidence would be presented) were executed (9). A panel of key expert stakeholders in the evidence outcomes should have been formed to formalize a set of themes for systematic synthesis and the application of other research methods; for example, a consensus development using techniques such as the Delphi method (10). As a consequence, key fundamental research papers were omitted,

including EU studies. Given the many methodological deficiencies in the Opinion, the conclusions cannot be accepted with any confidence and refer SCHEER to the attached literature.

Ref:

1. Carmines EG, Zeller RA. Reliability and validity assessment. Beverly Hills, California: Sage Publications; 1979.
2. Quality AfHRA. Methods guide for effectiveness and comparative effectiveness reviews [Internet]. Rockville, MD; 2008.
3. Proykova A, Kraetke R, Bertollini R, Borges T, Duarte-Davidson R, Panagiotakos D, et al. Memorandum on weight of evidence and uncertainties. Revision. 2018.
4. Hartmann-Boyce J, McRobbie H, Lindson N, Bullen C, Begh R, Theodoulou A, et al. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews. 2020(10).
5. Schünemann H, Brożek J, Guyatt G, Oxman A, editors. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 20132013.
6. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;6(7):e1000100.
7. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017;358:j4008.
8. Pound L, Kim M, Steffensen I, Curtin G. Reporting and Methodological Quality of Systematic Reviews Evaluating the Associations Between E-Cigarette Use and Combustible Cigarette Smoking Behaviors: A Systematic Review. 2020. 202.

515	Lund Karl Erik,Norwegian Institute of Public Health,Norway	METHODOLOGY	It is not clear how the search of relevant literature used as scientific basis for chapter 6.6 (initiation and gateway theory) and 6.7 (e-cigarettes and smoking cessation) has been carried out. A number of relevant publications have been omitted on these subjects. The search terms should be transparent and included in the appendix.	Please see Table 1, answer 2.
516	Sproga Maris,Smoke Free Association of Latvia,Latvia	METHODOLOGY	Page 19, lines - 33-42 Lots of sources used by SCHEER discuss the situation in the United States, not in the EU. So it does not concerns EU regulations and situation, for instance the limit of 20mg/ml nicotine set by TPD. We do suggest that SCHEER's opinion should look more into the prevalence and usage of e-cigarettes in the EU countries.	Please see Table 1, answer 8.
517	Brose Leonie,King's College	METHODOLOGY	The methods are insufficiently described and what is described has considerable weaknesses, making it questionable whether the work undertaken was adequate to address the terms of reference for this	Please see Table 1, answer 2.

London, United Kingdom

opinion. To highlight just some of the weaknesses:

- a. Established guidelines for systematically reviewing evidence and the reporting of reviews have not been followed.
- b. The cut-off date for literature to be included was April 2019, ie about 18 months before the publication of this preliminary opinion and likely about 2 years before the publication of the final opinion. This results in reliance on out-of-date data in the quickly moving field of e-cigarettes. The search needs to be updated before the publication of the final opinion.
- c. It is not reported which databases were searched.
- d. It is not reported what other methods were used to identify evidence. Mention of ‘further articles of importance’, ‘reports by other organisations’ suggests selective inclusion.
- e. It is unclear how the search terms in the appendix were used. If used as shown and ‘e-cigarette’ or ‘electronic cigarette’ was required in each scientific publication, this will have excluded scientific publications using eg ‘ENDS’, ‘ANDS’, ‘vaping products’ or any other term without also mentioning one of the two mentioned above.
- f. Problems with the use of search terms and databases are reflected in the initial search resulting in fewer than 4000 articles when the period of the search was not restricted. This is lower than the number of ‘hits’ to be expected with appropriate search terms and databases, indicating that relevant information is likely to have been missed.
- g. There is a lack of information about decision processes for inclusion and exclusion of scientific articles, e.g. what were inclusion criteria, how were articles screened, by how many reviewers. It is unclear how many articles were excluded and for what reasons.
- h. There is no information on consideration of the quality of the included articles, meaning that for example a small local study of a convenience sample could be given the same weight as a representative multi-country study.
- i. Summaries of evidence seem to have been copied without checking their primary sources, thereby copying any mistakes, misinterpretations or misrepresentations in the secondary sources into this opinion.

Please also refer to the SCHEER’s ‘Memorandum on weight of evidence and uncertainties - Revision 2018’, which is publicly available (https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_014.pdf).

			Any one of these weaknesses increases the risk of bias and reduces the reliability of the resulting evidence synthesis. In combination, these weaknesses appear fatal for the usefulness of this preliminary opinion.	
518	Brose Leonie, King's College London, United Kingdom	METHODOLOGY	<p>Page 19, lines 10-31 and Page 117, lines 2-53: The methodology in the text and the annex are insufficiently described and what is described has considerable weaknesses, making it questionable whether the work undertaken was adequate to address the terms of reference for this opinion. To highlight just some of the weaknesses:</p> <p>a. Page 19, lines 10-31: Established guidelines for systematically reviewing evidence and the reporting of reviews have not been followed (see eg https://training.cochrane.org/handbook/current or https://doi.org/10.1371/journal.pmed.1000097).</p> <p>b. Page 19, line 28: The cut-off date for literature to be included was April 2019, ie about 18 months before the publication of this preliminary opinion and likely about 2 years before the publication of the final opinion. This results in reliance on out-of-date data in the quickly moving field of e-cigarettes. The search needs to be updated before the publication of the final opinion.</p> <p>c. Page 19, lines 10-31 and Page 117, lines 2-53: It is not reported which databases were searched.</p> <p>d. Page 19, lines 29-30: It is not reported what other methods were used to identify evidence. Mention of 'further articles of importance', 'reports by other organisations' suggests selective inclusion.</p> <p>e. Annex 4, Page 117, lines 2-53: It is unclear how the search terms in the appendix were used. If used as shown and 'e-cigarette' or 'electronic cigarette' was required in each scientific publication, this will have excluded scientific publications using eg 'ENDS', 'ANDS', 'vaping products' or any term without also mentioning one of the two mentioned above.</p> <p>f. Page 19, lines 25-26: Problems with the use of search terms and databases are reflected in the initial search resulting in fewer than 4000 articles when the period of the search was not restricted. This is lower than the number of 'hits' to be expected with appropriate search terms and databases, indicating that relevant information is likely to have been missed.</p> <p>g. Page 19, lines 10-31: There is a lack of information about</p>	<p>Please see Table 1, answer 2.</p> <p>Please see Table 1, answer 6.</p>

decision processes for inclusion and exclusion of scientific articles, e.g. what were inclusion criteria, how were articles screened, by how many reviewers. It is unclear how many articles were excluded and for what reasons.

h. Page 19, lines 17-22: There is no information on consideration of the quality of the included articles, meaning that for example a small local study of a convenience sample could be given the same weight as a representative multi-country study.

i. Page 19, lines 27-31: Summaries of evidence were copied without checking their primary sources, thereby copying any mistakes, misinterpretations, misrepresentations or ‘spin’ in the secondary sources into this opinion.

Any one of these weaknesses increases the risk of bias and reduces the reliability of the resulting evidence synthesis. In combination, these weaknesses appear fatal for the usefulness of this preliminary opinion

Ref:

Moher (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Medicine. July 2009 | Volume 6 | Issue 7 | e1000097

<p>519 Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU</p>	<p>METHODOLOGY</p>	<p>The preliminary SCHEER Opinion report does not meet SCHEER’s standard: “Clear and transparent documentation and argumentation is essential for allowing stakeholders and policy-makers to understand how the lines of evidence were selected, assessed and integrated in the WoE used by the SCHEER for the development of the Scientific Opinion. More specifically, what is needed is explicit and transparent documentation of the assumptions, defaults, data sources, decision criteria, applications of expert judgment and other descriptive information used to reach the conclusions of the assessment. The rationale should include any uncertainties and gaps.”</p> <p>SCHEER, Memorandum on weight of evidence and uncertainties - Revision 2018 (cited by SCHEER) We therefore ask the SCHEER to much better explain in its final Opinion how the lines of evidence were selected, assessed and integrated and to clearly detail and explain the assumptions, defaults, data sources, decision criteria, applications of expert judgment especially in regard of the value of non-EU evidence and the lack of comparison between vaping and</p>	<p>Please see Table 1, answer 2.</p>
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smoking.

On the value of non-EU evidence and the lack of comparison between vaping and smoking, the preliminary SCHEER Opinion doesn't follow the SCENIHR (2012) guidelines for a good risk assessment:

“A good risk assessment must ensure that the parameters considered are relevant, the findings are clear, properly disseminated and provide a sound basis for actions, where needed. It is important that stakeholders, in particular risk managers are involved with the risk assessment process, without distorting its scientific objectivity. Risk assessment needs to be couched in terms that are clear and provide a valued basis for actions. The risk assessment paradigm needs to take into account ways in which a risk can be helpfully contextualised:

- Against an agreed acceptable risk benchmark: At present, in Europe there is no definition of acceptable risk. Instead, it is often based solely on the application of very conservative, non-scientifically derived default factors. This is an issue that requires a dialogue among all stakeholders since its implications are much more far reaching than the domain of science!
- By comparison with other relevant risks: This requires an available validated database of risk assessments so that the most appropriate ones can be used for comparison purposes.
- Using a risk benefit/cost benefit framework: Some of the European societies are considerably more risk averse than it is generally the case in the USA and many other countries. A presentation of risks devoid of any consideration of either the cost of risk reduction or of the benefits serves to reinforce risk aversion among politicians and the public. Cost-benefit analysis is one way of seeking to balance the benefits and costs of using chemicals and other stressors with hazardous substances.” SCENIHR, New Challenges for Risk Assessment, 2012, page 20.

We therefore ask the SCHEER to include in its final Opinion a clear comparison with other relevant risks (especially smoking risks) and to publish a risk benefit/cost benefit framework.

Please see Table 1, answer 1.

Page 19 / Lines 29-31
For purposes of transparency, we ask the SCHEER which

			<p>organisations reported and how? What information did the Commission provide?</p> <p>Page 19 / Lines 33-42</p> <p>Considering that this Opinion relies massively on US data and “trends”, the SCHEER should clearly state here that the US does not have the high-level health protection regulation provided by the TPD. It should be clearly stated throughout the whole Opinion each time US data are used to assess a risk.</p> <p>Ref: SCENIHR (2012). Addressing the New Challenges for Risk Assessment.</p>	
520	Pooler Marc,UK Vaping Industry Association,United Kingdom	METHODOLOGY	<p>The opinion says that conclusions were reached on the basis of a weight of evidence (WOE) approach. The WOE approach used is not transparent.</p> <ul style="list-style-type: none"> • A WOE approach implies that all relevant scientific evidence was used, and the term ‘weight’ implies that all data do not contribute equally to addressing a particular hypothesis. • Page 10, lines 3-4 – The terms of reference of this report also clearly state that ‘the main purpose of the scientific opinion is to assist the Commission in assessing the most recent scientific and technical information on e-cigarettes.’ • It is clear that ‘all relevant’ and ‘most recent’ scientific and technical information was not used to create this report: <ul style="list-style-type: none"> o Studies conducted by regulatory authorities or relevant bodies in member states on TPD including, for example, the most recent recent Public Health England report.. o Section 6.5.4, page 51 – Literature not relevant to e-cigarettes was cited in some cases. For example, cited literature on second-hand exposure references combustible cigarettes, not e-cigarettes. o Much of the opinion is based on evidence from the US on US products, not available to EU citizens and not TPD compliant. o Much of the cited literature is old and therefore includes information on dated products that are no longer available and on products that were sold before implementation/transposition of TPD2 and are therefore irrelevant. 	<p>Please see Table 1, answer 8.</p> <p>The list of references has been published.</p>
521	Pooler Marc,UK Vaping Industry	METHODOLOGY	<p>The opinion says that conclusions were reached on the basis of a weight of evidence (WOE) approach. The WOE approach used is not transparent.</p> <ul style="list-style-type: none"> • A WOE approach implies that all relevant scientific evidence was 	<p>See the reply to comment 520.</p>

<p>Association, United Kingdom</p>		<p>used, and the term ‘weight’ implies that all data do not contribute equally to addressing a particular hypothesis.</p> <ul style="list-style-type: none"> • Page 10, lines 3-4 – The terms of reference of this report also clearly state that ‘the main purpose of the scientific opinion is to assist the Commission in assessing the most recent scientific and technical information on e-cigarettes.’ • It is clear that ‘all relevant’ and ‘most recent’ scientific and technical information was not used to create this report: <ul style="list-style-type: none"> o Studies conducted by regulatory authorities or relevant bodies in member states on TPD including, for example, the most recent Public Health England report. o Section 6.5.4, page 51 – Literature not relevant to e-cigarettes was cited in some cases. For example, cited literature on second-hand exposure references combustible cigarettes, not e-cigarettes. o Much of the opinion is based on evidence from the US on US products, not available to EU citizens and not TPD compliant. o Much of the cited literature is old and therefore includes information on dated products that are no longer available and on products that were sold before implementation/transposition of TPD2 and are therefore irrelevant. 	
<p>522 Froguel Alizee, Cancer Research UK, United Kingdom</p>	<p>METHODOLOGY</p>	<p>Cancer Research UK is concerned that this report cites and therefore potentially bases aspects of the Committee’s preliminary opinion on a number of tobacco industry-funded studies (like in p66 131-35 for instance). It is important that all the evidence cited in this opinion and therefore available to inform policy makers responsible for regulating e-cigarettes is completely independent from the vested interests of the tobacco industry. Cancer Research UK believes that this report should exclude from its analysis any study that is fully or partly funded by tobacco companies or their affiliates.</p> <p>Indeed, Article 5.3 of the WHO Framework Convention on Tobacco Control states that “in setting and implementing [...] public health policies with respect to tobacco control, Parties shall act to protect these policies from commercial and other vested interests of the tobacco industry in accordance with national law”. It is imperative that the tobacco industry’s involvement in the e-cigarette market, and consequently in e-cigarette research, does not provide them with an opportunity to participate as a stakeholder in</p>	<p>Please see Table 1, answer 2.</p>

public health policy. Using evidence funded by the industry risks undermining the goals of the Convention, and in particular Article 5.3.

523	Vobořil Jindřich, Institute for Rational Addiction Policies, Czech Republic	METHODOLOGY	<p>Page 19 lines 28-29, 33</p> <p>The segment of electronic cigarettes, as well as information on their use, is evolving very rapidly. Therefore, SCHEER opinion should take into account the most up-to-date studies that are available.</p> <p>Page 19 lines: 33-42</p> <p>The SCHEER opinion very often refers to available studies for U.S. market that does not reflect the reality in the EU.</p>	<p>The text of the Opinion has been amended.</p> <p>Please see Table 1, answer 8.</p>
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524	McNeill Ann, King's College London, United Kingdom	METHODOLOGY	<p>Page 19 – General comments</p> <p>I am only commenting on the methodology section as I felt that the lack of clarity and comprehensiveness therein made it very difficult, if not impossible, to judge the other sections which would thus require line by line comments. I have previously been involved in a SCENIHR report and using my knowledge of that process to make these comments.</p>	
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Line 14 – as stated the methodology needs to be ‘transparent’ and ‘based on scientifically accepted approaches’, but I am afraid that there was a lack of clarity and transparency in key details here.

Line 21-22 The criteria of validity, reliability and relevance... quality has to be assessed. It is not clear how this has been carried out.

Line 24-31 and Annex 4. The methods described here missed important information on for example, how search terms were combined, the eligibility criteria, the electronic databases searched, selection process, data extraction, and the risk of bias and quality ratings. The search terms do not encompass all of the questions covered in the Opinion.

Line 28 – The start date of 01.01.2015 is perplexing. The TOR state that the opinion is ‘to assist the Commission in assessing the most recent scientific and scientific technical information on e-cigarettes ...to feed into the Commission’s reporting obligations under Article 28 of the TPD and help the Commission in assessing the

potential need for legislative amendments under the Directive..’ It is unclear why studies prior to the implementation of the TPD is included. There needs to be a clear rationale for this, given the changes that the TPD made to e-cigarettes on the market. In my view, you would need to be very cautious about making any conclusions based on studies carried out prior to implementation of the Directive. At the very least, studies should be clearly marked as to whether they are pre-TPD implementation.

Line 29. The statement ‘if necessary’ needs more explanation. What were the criteria for the choice of primary sources? Some key papers during the period studied are omitted.

Line 30. ‘SCHEER made use of reports by other organisations on this topic’ – again this needs to be made clear. How were these reports located? As part of the search strategy?

Line 33-42. Use of US data. The committee has noted caveats around the use of US data. However, similar to the point above, including US data particularly on product content, exposure and use would seem very inappropriate when the purpose of this Opinion is to inform the Commission’s review of the EU TPD. There are very clear differences in the products on the US and European markets. This is relevant to all chapters. For example, research on youth use of e-cigarettes from the US which has a much higher nicotine cap than Europe is not generalisable to Europe -for example the nicotine cap might affect addictive potential. Products used by adult smokers for cessation will also therefore differ, and likely biomarker exposure. The comment about 'trends spilling over to the EU, even if new products have to be adapted' is inappropriate in such a scientific report which is specifically about products governed by the EU TPD.

Please see Table 1, answer 8.

Finally, and most importantly, the methodology does not make any reference on comparisons with tobacco cigarettes and how these are made and to what extent smoking studies were included in the search strategy. Given electronic cigarettes were introduced to help smokers to stop, the relative risks with tobacco cigarettes need to

Please see Table 1, answer 1.

525	Atakan Tekin,Independent,Sweden	MINORITY OPINIONS	<p>be considered in addition to any absolute risks of electronic cigarettes and not doing so is a real weakness of the Opinion.</p> <p>This is only a test to see how the functionality is as the instructions are somewhat lacking and for us it is crucial to get our entire point across. In most cases we as consumers are considered stooges of industry and thus banned from entering any premises where discussions specifically about us are taking place. Very similar really to the Saudi commission on women's rights on which of course no women can serve as that would be inappropriate. so if you read this then please discard but at same time note that this is extremely discriminatory behaviour against a group who are 1.4 billion strong.</p>	Thank you for your comment.
526	Woessner Julie,International Network of Nicotine Consumer Organisations (INNCO)	MINORITY OPINIONS	<p>On a topic with a high polarization of the debates in the scientific world (see Bell, 2014), it seems strange that no minority opinion existed within the SCHEER.</p> <p>“Transparency should be ensured and the Opinions of the Scientific Committee shall include any minority Opinions, together with scientific supporting argumentation. Minority Opinions can only be expressed by members and shall be attributed accordingly.”</p> <p>SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Guidance on structure and content of SCHEER documents, 2017 (cited by SCHEER).</p> <p>Ref: Bell (2014). All gates lead to smoking: The ‘gateway theory’, e-cigarettes and the remaking of nicotine. https://doi.org/10.1016/j.socscimed.2014.08.016</p>	The SCHEER resolved all discussion points and found common conclusions , so there was no need for a minority Opinion within the SCHEER.
527	Compernelle Thomas,British American Tobacco,Belgium	MINORITY OPINIONS	<p>Remarkably, the SCHEER Preliminary Opinion does not include any minority opinions from the Committee. Other expert opinion and policy advisory document to date, prepared by expert bodies and regulatory agencies globally, have appropriately included extensively documented discussions acknowledging the public health principle of tobacco harm reduction and the consideration of e-cigarettes as a lower-risk alternative for smokers. The Opinion entirely neglects this important concept, and this ‘elephant in the room’ must be appropriately acknowledged and discussed. The Opinion’s provision for Minority Opinions presents an opportunity to correct this important oversight by providing a truly balanced</p>	<p>Please see Table 1, answer 2.</p> <p>As regards harm reduction, see Table 1, answer 1. Additional literature provided in the public consultation was considered based on these criteria.</p> <p>The SCHEER resolved all discussion points and found common conclusions , so there was no need for a minority Opinion within the SCHEER. It should be</p>

representation of a substantial volume of the published, peer-reviewed literature that addresses the role of c-cigarettes as a potentially powerful tool to achieve reductions in the risks to individual smokers and in the harms to the EU population from cigarette smoking.

A growing number of comparative studies have reported reductions in exposures to harmful chemicals, reductions in toxicity and biological effects in smokers who switch to e-cigarettes. Though BAT do not market e-cigarettes as smoking cessation devices, the well-respected Cochrane Collection recently published a comprehensive evidence-based report concluding moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and NRT; none of the included studies (up to 2-years duration) detected serious adverse events related to e-cigarette use.

The US National Academies of Science, Engineering and Medicine acknowledged the potential public health benefit of e-cigarettes in a published Report. The Report Committee comprised 13 academic scientific experts having extensive records of peer-reviewed publications on e-cigarettes. The Report was rigorously peer-reviewed before publication and was generated by inviting stakeholders to bring their collective evidence to the discussions.

The UK Royal College of Physicians (RCP) provided a detailed expert interpretive review and analysis of peer-reviewed, published literature documenting the harm-reduction potential of e-cigarettes for smokers who adopt their use as a replacement for cigarette smoking. In addition, an expert body convened by Public Health England (PHE) has produced and annually updated a series of major reports on vaping in England that offers expert analyses of the impact of e-cigarette usage on the public health, most recently in March 2020. These RCP and PHE reports reflect the opinions and comprehensive published literature analyses from biomedical and public health experts who have followed and considered the entire spectrum of new scientific findings that document the impacts of e-cigarettes on public health. Importantly, these major, comprehensive expert reports provide a balanced perspective on

noted, that according to the Rules of Procedure, Minority opinions can only be expressed by the scientific committees' members.

both the potential harms and the potential benefits of e-cigarettes. This objectivity is conspicuously absent from the Opinion, and SCHEER is well advised to follow the precedents by including a balanced consideration of the potential of e-cigarettes to provide public health benefits by accelerating the decline of smoking in the EU that may arguably outweigh any potential risks that e-cigarette use may pose.

The Opinion, as drafted, is deficient in its failure to acknowledge and fairly consider the abundantly documented risk-reduction potential and societal public health benefits of e-cigarettes, and the addition of a balanced discussion of what SCHEER apparently regards to be a minority opinion is a necessary addition to the Report. We respectfully request SCHEER consider and refer to the growing literature.



ref-527.docx

528 Arffman Päivi, Vapers Finland, Finland RATIONALE 6.2. Design Features: "It should be noted, that the electronic cigarette brand with the largest US market share (~75% as of 2019 [...])." (Page 21, lines 25-26). The percentage is incorrect as it only takes into account sales in tracked channels like convenience stores and it doesn't take into account online sales or sales by electronic cigarette specialty stores. Ref: Levy (2019). Examining the relationship of vaping to smoking initiation among US youth and young adults: a reality check Glasser (not published). Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey

The text has been revised.

529 Arffman Päivi, Vapers Finland, Finland RATIONALE Use in young populations, children and adolescents (USA) (Page 26, line 27) The most important information is missing from this section, ie the figures describing the regular use of e-cigarettes. In 2018, of all middle- and high-school students in the United States, 3.6% used e-cigarettes regularly (≥20 days/month) and only 0.4% of never-smoking youth.

Please see Table 1, answer 8.

			<p>At the same time, with the increase in the use of e-cigarettes, young people's smoking has decreased two to four times faster than before. Currently, about one percent of U.S. youth smokes daily.</p>	
530	No agreement to disclose personal data	RATIONALE	<p>The document presents a very good analysis of the features and characteristics of e-cigarettes, incl. published effects on physiological and pathophysiological processes.</p> <p>The only objective for protection of public health is to definitively stop smoking, and that is the one and only objective of every physician. But when people cannot quit smoking, despite all possible efforts, then an alternative to stop smoking is sought. Authorized nicotine replacement therapies are an option, but they do not work with every smoker attempting to quit.</p> <p>Electronic cigarettes are also an alternative.</p> <p>The document is a very good example of explaining and illustrating with concrete data the side effects on health, but we accept that this is an alternative to smoking cessation, therefore a comparative analysis of parameters with traditional cigarettes should be made.</p> <p>In addition, there must be a differentiation between burning cigarettes, e-cigarettes containing liquid and heated tobacco products. The differences are huge, and let's not forget that the last two are not harmless, but are much less harmful than traditional cigarettes.</p> <p>However, their use is not recommended due to their harm to the body, but the transition from smoke to smokeless cigarettes (devices) and subsequent attempts to quit smoking.</p>	Thank you for your comment.
531	Martinez Javier, JT International SA, Switzerland	REFERENCES	<p>We respectfully ask SCHEER to refer to all studies that we uploaded in each of the sections that we commented. A complete list of references with full cites is uploaded here. Additionally, we note that there are several studies in SCHEER's references list that are not cited and commented in the report, including Burstyn et al. (page 74 line 28) ; Dana-Farber Cancer Institute (2019) ScienceDaily, 28. (page 76 line 2) Moreover, some references are incomplete, e.g., Long 2014. page 84 line 9. Please consider</p>	<p>Please see Table 1, answer 2.</p> <p>The reference list has been updated.</p>

			commenting on the these references listed in SCHEER reference list or amend as appropriate.	
532	Champagne ac Maxime, P hode, France	REFERENCES	<p>p91 lines 17-22 "Visser, W., Geraets, L., Bos, P., Ramlal, R., Fokkens, P., Klerx, W., Cremers, H., Schwillens, P. and Talhout, R. (2016). De gezondheidsrisico's van e-sigaretten voor omstanders [The health risks of electronic cigarette use to bystanders]. National Institute for Public Health and the Environment, Bilthoven, the Netherlands, RIVM rapport 2016-0036 (in Dutch), 2 Technical Appendix in English), Available from: http://www.rivm.nl/bibliotheek/rapporten/2016-0036.pdf "</p> <p>https://www.rivm.nl/bibliotheek/rapporten/2016-0036.pdf</p> <p>The scenario with 50% nicotine exhaled like in smoke isn't applicable to the vapor as 95% of the nicotine is absorbed similar https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/</p> <p>p91 lines 24-26 "Visser, W.F., Klerx, W.N., Cremers, H.W.J.M., Ramlal, R., Schwillens, P.L. and Talhout, R. 24 (2019) The health risks of electronic cigarette use to bystanders. International Journal of 25 Environmental Research and Public Health 16: 1525. doi.org/10.3390/ijerph16091525 26"</p> <p>Why the study was made with products with tobacco extract ? not relevant. for products without tobacco extract. It shouldn't be used for the overall risk assesment.</p> <p>It is precised in this study the Regulatory Implications part.</p> <p>Considering that only a limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU.</p>	<p>Please see Table 1, answer 2.</p> <p>The reference list has been updated.</p>
533	Champagne ac Maxime, P hode, France	REFERENCES	<p>p91 lines 24-26 "Visser, W.F., Klerx, W.N., Cremers, H.W.J.M., Ramlal, R., Schwillens, P.L. and Talhout, R. 24 (2019) The health risks of electronic cigarette use to bystanders. International Journal of 25 Environmental Research and Public Health 16: 1525. doi.org/10.3390/ijerph16091525 26"</p> <p>Why the study was made with products with tobacco extract ? not relevant. for products without tobacco extract. It shouldn't be used for the overall risk assesment.</p> <p>It is precised in this study the Regulatory Implications part.</p> <p>Considering that only a limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU.</p>	<p>See Table 1, answer 4.</p>
534	O'Leary Renee, Center of Excellence for the	REFERENCES	<p>Please note that several studies in our reference lists in the comment sections could not be uploaded due to file size. Items noted in Preliminary Opinion References 21 articles are listed in the References but are not cited in the Preliminary Opinion</p>	<p>Please see Table 1, answer 2.</p> <p>The reference list has been updated.</p>

Accelerati
on of
Harm
Reduction,
University
of Catania,
Italy, Italy

P. 73 L35 Benowitz and Fraiman (2017)
P. 73 L54 Bhatnagar et al. (2014)
P. 74 L13 Brown et al. (2016)
P. 74 L28 Burstyn (2014)
P. 74 L 35 Callahan-Lyon (2014)
P. 74 L 42 Cervellati et al. (2014)
P. 76 L2 Dana-Farber Cancer Institute (2019)
P. 80 L11 Grana et al. (2014)
P. 81 L37 Huang et al. (2017)
P. 83 L8 Kumar et al. (2019)
P. 85 L51 McNamee (2014)
P. 85 L14 Moore et al. (2009)
P. 86 L22 Palazzo (2013)
P. 87 L16 Ren and Lotfipour (2019)
P. 89 L5 State Health Officer's Report (2015)
P. 89 L20 Stratton (2018)
P. 89 L25 Syamlal et al. (2016)
P. 89 L29 Talhout et al. (2011)
P. 89 L56 Tobore (2019)
P. 92 L26 Wong et al. (2015)
P. 92 L33 Zainol et al. (2017)
4 articles are listed twice
P. 82 L20 and L25 Ki-Hyun et al. (2016) Review of Electronic Cigarettes
P. 82 L45 and L53 Kosmider et al. (2014) Carbonyl Compounds
P. 83 L34 and L41 Lee et al. (2018) Latent Class Analysis
P. 92 L7 and L22 Williams et al. (2013) Metal and Silicate
3 references have a last name and a year and no other information
P. 81 L51 "Jamal 2017"
P. 84 L9 "Long 2014"
P. 84 L49 "McConnell 2015"

535 Schulz
Thomas,G
erman
Federal
Institute
for Risk
Assessmen
t,Germany

REFERENCES

P84, Row 28-29, Mallock 2020 reference
The full reference is: Mallock N, Trieu HL, Macziol M, Malke S, Katz A, Laux P, Henkler-Stephani F, Hahn J, Hutzler C, Luch A (2020) Trendy e-cigarettes enter Europe: chemical characterization of JUUL pods and its aerosols. Arch. Toxicol. 94: 1985-1994.
P84, Row 49, McConnel 2015 reference
The reference is incomplete and it is missing in the full text of the

Thank you for your comment.

			report.		
			P89, Row 29-32 Talhout 2011 reference There is no use of this reference in the report.		
536	Balsam Paweł, Warsaw Medical University, Poland	REFERENCES	I suggest to include the FDA decision on IQOS authorization https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information AVAILABLE EVIDENCE TO DATE: The IQOS system heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.”	Please see Table 1, answer 2. The reference list has been updated.	
537	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	REFERENCES	Page 74 / Lines 2-3 Using unpublished evidence for risk assessment contradicts the SCHEER/SCENIHR guidelines on transparency.	All studies have been published with the exception of Bos et al., which is submitted for publication and us under review.	
538	Moiroud Jean, Fédération Interprofessionnelle de la Vape	REFERENCES	P. 91, lines 12-15: A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids. P. 91, lines 17-22: Regarding this reference, the scenario with 50% nicotine exhaled like in smoke isn't applicable to the vapour as 95% of the nicotine is absorbed. Furthermore, 89% of PG and 92% of	For TSNAs: see Table , answer 4. See Table 1 answer 4.	

(FIVAPE),
France

VG is being inhaled while vaping, which only accounts for an exhale of 11% and 8% (respectively). Please see: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/>

P. 91, lines 24-26: Considering that only a limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU.

Ref:

St Helen et al. (2016). Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/>

See Table 1, Answer 4.

539 Compernelle
Thomas, British
American Tobacco,
Belgium

REFERENCES

The references section is one of the most important parts of an opinion or review article, as it clarifies the source of scientific fact and information. However, the Reference Section in the Opinion does not represent an unbiased cross-section of research – see statistics below. Specifically, only ~3% of references come from industry. Nearly half of the references are reviews covering many of the same (dated/older) primary studies, and the number of cited references with more current EU-marketed products are proportionally low (only 4% of references from 2020). Among the publications from academia, there is a bias towards studies originating from the US in general, but some of the individual EU academic labs are also over-represented (e.g. 14 references from Farsalinos lab). Finally, unpublished peer-review findings (a mix of unpublished studies, opinions, workshop reports and white paper - letters to the editor, etc.; e.g. McNamee p. 84) account for roughly 5% of the references. Although these non-peer-reviewed documents/publications add value and perspective, they should be used to support conclusions and not to derive them.

The Opinion's treatment and interpretations of systematic reviews are also inconsistent. Specifically, the Opinion reviewed several systematic reviews in Section 6.6, but there is no reference to a GRADE approach for the quality of evidence assessment. In Section 6.7, the Opinion specifies a GRADE rating for two systematic reviews; additionally, PRISMA guidelines and AMSTAR 2 would have rated the methodological and reporting quality of the reviews. This approach should have been applied throughout this evidence synthesis.

This section could benefit from additional attention to detail and format. Multiple errors and mistakes were noted, including inconsistencies in

The SCHEER refers to the methodology section 4, explaining that a literature search was performed until April 2019. The search terms used are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019. In addition, the SCHEER made use of reports by other organizations on this topic, as well as on information provided by the Commission. Additional literature provided in the public consultation was considered based on these criteria.

The SCHEER refers to the methodology section 4, explaining that a literature search was performed until April 2019. The search terms used are listed. To cope with the huge amount of scientific publications, the SCHEER used firstly review articles published between 01.01.2015 and April 2019. If necessary, the primary sources were also used, as well as further articles of importance published after April 2019. In addition, the SCHEER made use of reports by other organizations on this topic, as well as on information provided by the Commission. Additional literature provided in the public consultation was considered based on these criteria.

Please see Table 1, answer 2.

format style (e.g. 2 Etter et al. refs., P77), a number of duplications (e.g. Kim et al., P82), references published in more than one language at different times pointing to the same primary studies and drawing similar conclusions (e.g. Visser et al., P91), mislabeled/incorrect publication dates (e.g. Lee et al., P83, LN34 year is 2019), lack of full or correct citation details (e.g. Long, P84) and e-pub ahead of print citations used for publications dating back to 2016 (e.g. Malas et al., P84).

The reference list has been updated.

A large body of scientific evidence has not been considered by SCHEER, in particular the most recent scientific information. We respectfully request that SCHEER disclose the criteria used to select the scientific literature and also the methodology to evaluate the strength of the scientific information to inform this Opinion. We kindly refer SCHEER to the references provided to support the re-evaluation of their conclusions.

Author Affiliation – Institution/Organization:
 Academia 61% ; Industry 3% Public Health/Govt ; 20%
 Other/Mixed/Unknown ; 16% Country of Origin: U.S.
 35% Non-U.S. ; 65% Type of Publication: Standard/Guide/Position
 14% Review ; 28% Unpublished/Non-peer reviewed ; 5% Primary
 Research (not tabulated, but all remaining) ; 52% Year of Publication:
 Published 2014-2019 (stated target) 80% ; Published 2020 (most current)
 4% ; Published before 2014 (possibly irrelevant or outdated) 16%



8_References_-_All_C
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540 CANINO SCIENTIFIC
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 E,Associazione
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Approximately 1.200 pro e-cig studies carried out between 1947 and 2019 are attached in two pdf file!

Thank you. For the literature selection: see Table 1, Answer 2.

541 Pierantoni SCIENTIFIC
 Nicola,eur OPINION
 opean

Il vaporizzatore personale aiuta a smrttere di fumare

Thank you. For the literature election: see Table 1, Answer 2.

	citizen,Italy								
542	oberhoff peter,me, Germany	SCIENTIFIC OPINION	it helped me quit smoking 100%						Thank you for your comment.
543	Bernhard-Michael Mayer,University of Graz, Pharmacology and Toxicology,Austria	SCIENTIFIC OPINION	40 years of at last 50 cigs	page 12,	lines	19-27			E-cigarette droplets contain chemicals that can have different origin: i) from e-liquids (propylene glycol, glycerol, nicotine, water, flavourings, preservatives); ii) formed by chemical reaction or thermal decomposition in the heating element of some of constituents or solvent carriers (e.g. aldehydes, free radicals and reactive oxygen species, furans, acetic acid); iii) originating from the device (e.g. metals).
			The SCHEER appears to lack basic knowledge in biophysics: line 24: "No clear data can be found whether the particle fractions detected are liquid or solid..." Any expert committee worthy of that name should know that aerosols generated in the absence of combustion don't contain solid particles. This conclusion is evident for e-cigarettes, which produce vapor (fog, mist) by heating liquids. Sophisticated experimental work shows that the conclusion is also valid for the aerosol generated by heating tobacco to about 300 °C [2].						It is correct that droplet/particle size defines the site of deposition. But no clear data can be found on the nature of the metals in the aerosol (particle or ions in a liquid) this is described in section 6.5.2.1
			line 30: the SCHEER continues misleading readers by stating that the exhaled air of electronic cigarette users contains particulate matter. This statement is formerly true because the scientific term "particulate matter" includes solid and liquid particles in a gas. However, throughout the scientific literature and public interpretation, this term refers to the harms of air pollution caused by combustion smoke and not to aerosols generated by vaporizers.						It is correct that (exhaled) aerosols contain particulate matter, including liquid and solid particulates
			page 13,	lines	8-9				The mentioned line is a quote of a WHO report (as cited in the Opinion)
			"...electronic cigarettes still "are harmful to health and are not safe." This statement applies to everything in human life and, therefore, is a meaningless eternal truth, frequently used to unsettle policymakers and the public about the health benefits of e-cigarettes.						

			<p>Untenable claims on nicotine toxicity and the alleged harmful effects of e-cigarettes in the cardiovascular system and the airways are discussed in my replies to other report sections.</p> <p>1. Martuzevicius et al. Nicotine Tob. Res. 21, 1371-1377 (2019)</p> <p>2. Pratte et al. Hum. Exp. Toxicol. 36, 1115-1120 (2017)</p>	See answer to comment 159.
544	Spina Francesco, privateat,Italy	SCIENTIFIC OPINION	<p>Page 14 lines 52 to 56</p> <p>Overall assessment for electronic cigarette users</p> <p>Attached the study which the conclusion is:</p> <p>In this cohort study, use of ECs alone was not associated with an increased risk of wheezing among adolescents when other risk factors for respiratory symptoms were controlled. The findings suggest that other risk factors, including secondhand smoke exposure, may be associated with the development of negative respiratory symptoms among adolescents. So it's second hand smoke to be the cause of respiratory symptoms not vaping, it's quite clear!</p>	Thank you for submitting this publication. However, the SCHEER cannot support this paper and your conclusion. It is noted that the authors used data from a well known study, the PATH, in the field of tobacco use and health. The SCHEER has concerns: among others that the categorization "Time in close contact with a smoker in past 7 days" should have been used as a moderator and not as a covariate. The intercorrelation between EC use and close contact with a smoker may have prevailed the true effect of EC use. Table 1 should be in the format of asthma vs., not asthma and the exposures as independent vars ... but his way the reader could understand the crude associations, before reading the (problematic) multi-adjusted analysis.
545	Martinez Javier, JT International SA, Switzerland	SCIENTIFIC OPINION	<p>P.19, l.1-2 Please revise the statement "Taking into account data from cohort studies and randomised control trials, the weight of evidence for smoking cessation is weak to moderate..." Based on the scientific literature available, the evidence should not be reported as "weak". Please refer to the recent Cochrane Review concluding, "we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT" (Hartmann-Boyce et al. 2020) and to our extensive references provided in section 6.7. P.70, l.19-28</p> <p>P.13, l.40-43 Please revise these lines and the statement, "it can be assumed that similar mechanisms exist regarding the exposure to nicotine from electronic cigarettes use." This is misleading as e-cigarette aerosol is qualitatively and quantitatively different compared to cigarette smoke. E-cigarettes do not contain tobacco and no combustion takes place. There is no compelling evidence that nicotine might be a risk factor for the development of cardiovascular disease. The speculative nature of the SCHEER statement is inconsistent with the scientific literature which indicates there is no increased cardiovascular risk of nicotine exposure in consumers who have no underlying cardiovascular pathology. Please refer to our comprehensive peer-reviewed study of the literature (Price & Martinez 2020) noting, "there is not enough evidence to suggest that there is an increase in risk to long-term cardiovascular health as a result of nicotine exposure from either NRT or e-cigarettes [...]. Overall, current studies indicate that the nicotine delivered by e-cigarettes does not increase</p>	See Table 1, answer 6.
				This sentence has been revised accordingly.

the risk of cardiovascular events in individuals who do not have any underlying cardiovascular disease.” This is consistent with a recent COT report, which assessed the potential risk to health from nicotine and non-nicotine e-cigarettes, stating “No data were identified regarding repeated or long-term inhalation exposure to nicotine per se in humans and data on longer term effects of nicotine exposure from ENDS are not currently available.”

P.15, 1.1-14 The statement, “the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong” is inconsistent with the evidence presented in available studies. Based on the scientific studies available, the evidence should not be qualified as “strong”. To date, the evidence for effects of e-cigarettes on long-term cardiovascular health in adult smokers who have switched to e-cigarettes is inconclusive. SCHEER omitted a significant amount of the scientific literature regarding the cardiovascular effects of e-cigarettes. Please refer to our extensive comment and additional scientific studies provided under section 6.5.4 p.47, 1.27 onwards. Please amend as “insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function.” SCHEER notes 1.9-11, “The level of evidence regarding the cardiovascular effects of nicotine contained in electronic cigarettes and the related pathophysiological mechanisms is considered from moderate to strong.” Please revise this statement indicating that there is no increased cardiovascular risk of nicotine exposure in consumers who have no underlying cardiovascular pathology.

P.18, 1.18 Please revise and amend the statement, “Overall, the SCHEER is of the opinion that there is strong evidence that electronic cigarettes are a gateway to smoking for young people.” SCHEER interpretation of the evidence to support and qualify that vaping serves as a “strong” gateway to smoking is unconvincing. Please refer to our extensive comment and additional scientific studies provided in relation to P.67, 1.26 onwards.

Ref: COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Statement on the potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes)

Hartmann-Boyce (2020) Electronic cigarettes for smoking cessation (Review)

Price (2020) Cardiovascular, carcinogenic and reproductive effects of nicotine exposure: A narrative review of the scientific literature

Page 13, Lines 5-9: Public Health England established already in 2015 that vaping is 95% less harmful - and confirmed in 2020 [1] [2] that vaping has a small fraction of the risks of smoking.

See Table 1, answer 5.

See Table 1, answer 1.

546 Landl Michael,W orld SCIENTIFIC OPINION

Vapers'
Alliance,
Austria

Governmental agencies in Canada [3] and New Zealand [4] came to the same conclusions. Therefore it is baffling that this report is ignoring this evidence almost completely.

Page 13, Lines 36-38: Nobody argues that vaping has no risks at all, but the key question is, how does vaping compare to smoking? The studies above give a clear picture. It is far less harmful than smoking. Also it is established that the risk of cancer from e-cigarettes compared to that from smoking is less than half a percent [5]. Therefore, vaping is an important tool to improve public health.

Page 18, Lines 35-39: As already mentioned, only 2,1% of non-smoking [6] individuals surveyed frequently used e-cigarettes. The data from Action on Smoking and Health (ASH) UK [7] reports similar findings and states that youth smoking rates are at an all-time low and youth use of e-cigarettes is rare and most users are current or former smokers. Also flavours are not a main reason why adolescents start using e-cigarettes. Curiosity is the main driver for young people to start vaping. Outlawing curiosity will not be possible. Therefore, public policy must aim to improve life circumstances for those adolescents who have higher tendencies for riskier behaviour (household income, anxiety, problems in school, etc.)

Besides clinical studies demonstrating their effectiveness (quoted above), millions of former smokers to the contrary debunk this concern.

Page 19, Lines 1-7: There are a number of studies showing that e-cigarettes are by far the most efficient means for smokers to quit and have thus far done so for millions of users globally. A British Medical Journal study [7] examined whether the increase in use of e-cigarettes in the USA was associated with a change in overall smoking cessation rate at the population level. It found that the increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level. Another study [9], led by Queen Mary University of London Professor Peter Hajek found that vapour products are almost twice as effective for smoking cessation than nicotine-replacement therapy.

References:

See Table 1, answer 5.

See Table 1, answer 6.

[1][2] Ann McNeill, Leonie Brose., Robert Calder., Linda Bauld Debbie Robson, Vaping in England: an evidence update including mental health and pregnancy, March 2020;

[3] Government of Canada, Vaping and quitting smoking

[4] Ministry of Health, New Zealand, Supporting smokers to switch to significantly less harmful alternatives

[5] Stephens WEComparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smokeTobacco Control 2018;

[6] Martin Jarvis, Sarah Jackson, Robert West, Jamie Brown. (2020). Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA?

[7] Action on Smoking and Health, New ASH data reveals that youth use of e-cigarettes in Great Britain is very low

[8] Zhu Shu-Hong, Zhuang Yue-Lin, Wong Shiushing, Cummins Sharon E, Tedeschi Gary J. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys BMJ 2017

[9] Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy, N Engl J Med 2019;

547	Adam Bartha,EPI CENTER - European Policy Information Center,Belgium	SCIENTIFIC OPINION	<p>Christopher Snowdon, Head of Lifestyle Unit at the IEA, has provided a detailed rebuttal of several claims made in the SCHEER preliminary opinion. For the detailed analysis, please refer to the PDF attachment.</p> <p>The authors of the SCHEER report appear to be biased against e-cigarettes and harm reduction. The report reheats several arguments, such as the ‘gateway effect’ and the ‘renormalisation’ hypothesis, which are now a decade old and have been contradicted by real world evidence. While it downplays strong evidence showing that e-cigarettes have been a gateway from smoking for millions of people, it amplifies speculation about hypothetical risks. When the authors are unable to find adequate evidence for anti-vaping claims, they quote from organisations which share the same prejudice. Much of the evidence is treated selectively and some of the conclusions made about the strength of evidence are baffling.</p>	See Table 1, Answer 1
	A_response_to_the_SCHEER_preliminary_o			
548	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>Overall assessment for electronic cigarette users p15 lines 5-6 : "The overall weight of evidence for rosk* of long-term systemic effects on the 5 cardiovascular system is strong" (*rosk instead of risk)</p> <p>This statement should be revised as the evidences are for e-cigarette</p>	The Opinion has been revised accordingly regarding the health effects of electronic cigaretees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

with nicotine only. And the risk should be evaluated with products which are allowed on the European market with nicotine content lower than 20mg/mL. In Europe evaluating the risk for product at higher level of nicotine (ie 24mg/ml) is for pharmaceuticals not electronic cigarettes.

549	Champagnac Maxime, PhD, France	SCIENTIFIC OPINION	Overall assessment for second-hand exposed persons p16 line 2-3 "The overall weight of evidence is moderate for risk of local irritative damage to the 2 respiratory tract" For second hand exposure, the risk should be evaluate with realistic second hand exposition. The level of PG and VG adsorption is around 90% thus only 10% is released to the ambient atmosphere. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/	The risk assessment is based on measured concentrations.
550	Champagnac Maxime, PhD, France	SCIENTIFIC OPINION	p16 lignes 12-13 "The overall weight of evidence for risk for systemic cardiovascular effects in second-hand exposed persons due to exposure to nicotine is weak to moderate." For second hand exposure, the risk should be evaluate with realistic second hand exposition. The level of Nicotine adsorption is around 96% thus only 4% is released to the ambient atmosphere. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/	Please see Table 1, answer 4, 2 nd paragraph.
551	Champagnac maxime, PhD, France	SCIENTIFIC OPINION	p16 lines 21-25 "- The overall weight of evidence for a carcinogenic risk due to cumulative exposure to 21 TSNA is weak to moderate. The lines of evidence are the following: o Nitrosamines have been identified as genotoxic and carcinogenic. o The MoEs calculated for the carcinogenic risk from TSNA are low. o Human evidence is lacking." TSNA are only coming from tobacco extracts (not from nicotine with pharma grade (high level of purity as regulated). It is not fair to consider in the electronic cigarette overall assessment that all products have the potential to expose to TNSA but only products containing tobacco extracts and they should be regulated. Visser et al 2019, in "Regulatory Implications" chapter " Firstly, the levels of tobacco-specific nitrosamines in exhaled vapor are high enough	See Table 1, answer 4.

			that an elevated risk of cancer could not be excluded. Considering that only a limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU.	
552	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p18 lines 35-36 "Overall, the SCHEER is of the opinion that there is strong evidence that electronic 35 cigarettes are a gateway to smoking for young people."</p> <p>This statement should be precised and revised . The Assesment was based on evidence comming from the US with popular products promoted with advertisement and with nicotine content up to 59mg/mL. Other source are relevant in Europe to reconsider the gateway risk .https://www.sciencedirect.com/science/article/pii/S0376871620300181#Highlights Conclusions</p> <p>Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes. Further studies should investigate the longer-term role of vaping on future smoking habits with the use of causal inference methods.</p> <p>Other sources should also be considered: https://onlinelibrary.wiley.com/doi/abs/10.1111/add.13924</p>	See Table 1, answer 5.
553	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p18 lines 36-37 "In addition, there is strong evidence 36 that nicotine in e-liquids is implicated in the development of addiction."</p> <p>This statement should be precised or revised.as it need to be evaluate only with products with nicotine content lower than 20mg/mL</p>	See Table 1, answer 9.
554	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p18 lines 37-39: "There is also strong evidence that flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation too"</p> <p>This statement should be implemented ""There is also strong evidence that flavours have a relevant contribution for attractiveness of use and initiation of electronic cigarette and smoking cessation , too</p>	See Table 1, answer 7.

Evidence that flavours have a relevant contribution to smoking cessation
<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

555	Champagnac maxime,Phode,France	SCIENTIFIC OPINION	<p>p19 lines 1-2 "Taking into account data from cohort studies and randomised control trials, the weight of evidence for smoking cessation is weak and for smoking reduction it is weak to moderate." This stateement should be updated taking in account other recent significant sources https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used</p> <p>Authors' conclusions: There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the degree of effect, particularly when using modern EC products</p>	See Table 1, answer 6.
556	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p31 lines23 -25</p> <p>The levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavours, and tobacco alkaloids in electronic cigarette aerosols vary greatly (Cheng, 2014), https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p> <p>This sources used in this report shouldn't be partially used, it is in contraction with (cheng,2014 statement) as TSNA and tobbaoco alkaloids are not always present. A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.</p>	Agreed and acknowledged in the Opinion.
557	Champagnac Maxime,P	SCIENTIFIC OPINION	<p>p32 Table 3</p> <p>https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p>	See Table 1, answer 4.

	hode,France		<p>A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.</p> <p>It was madewith product made before the TPD 2 implementation, and thus diethylene glycol shouldn't be part of aerosol composition table used for the risk assesment.</p> <p>A separete risk assesment should be done for product with tobacco extract leading to TNSA in aerosols</p>		<p>See Table 5 and the risk assessment section. Diethylene glycol is not included.</p> <p>See Table 1, answer 4.</p>
558	Champagnac Maxime,P hode,France	SCIENTIFIC OPINION	<p>p36 lines 5-8</p> <p>"Farsalinos et al(2015)analysed TSNAs, using a second-generation device and threecommercial e-liquids. No TSNAs were detected in the aerosol. Goniewicz et al. (2014)measured NNN at 0.8-4.3 ng/150 puffs and NNK at 1.1-28.3 ng/"</p> <p>This was realised with products produced before the TPD implementation.</p> <p>TSNAs should'nt be part of the risk assment for e-cigarette but only for product with tobacco extracts :https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf</p> <p>A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.</p>		<p>See Table 1, answer 4.</p>
559	Champagnac Maxime,P hode,France	SCIENTIFIC OPINION	<p>p37 lines 5-7</p> <p>"The relevant compounds for the RA in electronic cigarette aerosols are mainly the solvent carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs),..."</p> <p>TSNAs are relevant only if the product contains tobacco extracts</p> <p>"The relevant compounds for the RA in electronic cigarette aerosols are mainly the solvent carriers (glycols and glycerol), nicotine, flavourings (if added to e-liquid), nitrosamines (TSNAs) (if added tobacco extract are added to the e-liquids),..."</p> <p>Visser et Al 2014 it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those</p>		<p>See Table 1, answer 4.</p>

			substances were not demonstrably present in the great majority of liquids."	
560	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p37 lines 9-10 "The risk assessment will be based on the aerosol concentrations found in the Visser et al 9 study (2014 and 2015). "</p> <p>The risk assesment shouldn't ne made with nitroamines nor diethylene glycol. Visser et Al 2014 it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids."</p> <p>More over this study could be realised with products on the markets before the TPD implementation.</p>	<p>See Table 1, answer 4.</p> <p>See Table 5 and the risk assessment section. Diethylene glycol is not included.</p>
561	Champagnac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p38 lines 4-6 "In spite of the high overall variability of results, caused by unstandardized experimental settings and expressed by the large ranges reported, the quality and the consistency of the data selected is judged to be medium to high."</p> <p>This statement should be updated.For carbonyl emissions in order to avoid risk of dry puff condition, the generation process should a vaping machine (not a smoking machine) as defined in the ISO 20768. Smoking machine are used with device at the horizontal devices, when vaping machin allows puffing génération with a 45° (as e-cig are used) angle reducing risks of dry puff associated carbonyls generation (i.e AFNOR XP D90-300-3). Lots of laboratory studiees where not relevant for this point. Dry puff is an artefact of smoking machine and electronic cigarettes users are moving and wiking their resistance continuously, without exposing themselves to bad taste linked with the dry puffing. At the ISO level, for the interlaboratory studies for the determination of aldehydes in emissions need to use standard e-liquide doped with aldehydes because the generation of aldehydes isn't quantifiable and reproductible in electronic cigarettes. (On the contrary of Heated tobacco products)</p>	See answers to comments 72, 98, 120.
562	Champagnac maxime,Phode,France	SCIENTIFIC OPINION	<p>p38 lines 26 Table 6</p> <p>Nitroamines can only comes from E-liquids containing Tobacco extracts.</p> <p>Visser et Al 2014 it is said that "A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of</p>	See Table 1, answer 4.

<p>563 Champagnac Maxime,Phode,France</p>	<p>SCIENTIFIC OPINION</p>	<p>liquids. TNSA should be part of the overall risk assessment for electronic cigarette but only for those with tobacco extracts. p41 lines 34 to 41 "Besides possible toxic effects after inhalation, these chemicals may confer a characterising 34 flavour to the e-liquid meaning a clearly noticeable smell or taste as for maltol, menthol or vanillin, thus contributing to attractiveness of electronic cigarettes. Flavourings can stimulate electronic cigarette use, especially among vulnerable groups such as non-smoking adolescents, thereby increasing exposure to potentially toxic ingredients. Indeed, the flavours by providing a specific and standardised taste, makes an e-liquid unique and 3recognisable among the large variety of available brands, thus binding the consumer 40 (Havermans et al., 2019). "</p>	
		<p>It is the author personal statement not proven in this study should be part of the Scheer opinion This position "Because the vast range of flavoured e-liquids is attractive to vulnerable consumer groups (eg, adolescents and young adults), there is a clear need for regulation. " in Havermans & al.2019, isn't scientifically argued . (no citation) it is a personal statement of the authors arguing for a need of regulation using a comparison with flavoured cigarette which are proved to be addicted and unhealthy. It is not the aim of this study to prove flavor attractiveness in vaping product.</p>	<p>Please see reply to comment 131.</p>
<p>564 Champagnac Maxime,Phode,France</p>	<p>SCIENTIFIC OPINION</p>	<p>p49 line 9 "cardiac arrhythmias and elevated blood pressure (Moheimani et al., 2017)" This study is not relevant ,with only 43 participants. The control group is biased, (male /female ratio; former smoker ratio 10/16 vs 2/18; period of smoking cessation 2,3years vs 13 years). The cardiovascular effect could be linked to the past cigarettes consumption as there were 10(16) former smoker in the e-cig group and only 2(18) in the control group.</p>	<p>The Moheimani- study has been excluded from the Opinion.</p>
<p>565 Champagnac Maxime,Phode,France</p>	<p>SCIENTIFIC OPINION</p>	<p>p38 lines 26-28 "The acute sympathomimetic effect of nicotine containing electronic cigarette can possibly be associated with increased cardiac risk populations with and without known cardiac disease. (Moheimani et al., 2017)."</p>	<p>The Moheimani- study has been excluded from the Opinion.</p>

			Weak study shouldn't be considered on its own as there isn't good control group and it was realised with a very few participants.(male /female ratio; former smoker ratio 10/16 vs 2/18; period of smoking cessation 2,3years vs 13 years). The cardiovascular effect could be linked to the past cigarettes consumption as there were 10(16) former smoker in the e-cig group and only 2(18) in the control group.	
566	Champagne ac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p48 lines 30 to 33 "Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells. Most electronic cigarettes containing nicotine have a basic pH > 9, which seems to enhance the dosage of nicotine delivered (Stepanov and Fujioka, 2015)."</p> <p>A study from 2015 is not recent for a 10 years product old. This recent study should be considered to revise the position https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used What are the results of our review? The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes. // Authors' conclusions: [...]We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall number of studies was small.</p>	Please see the reply to comment 135 and 175.
567	Champagne ac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p48 lines 38-39 "leading to prolonged elevated systolic blood pressure (Franzen et al., 2018)."</p> <p>Study realised with 24mg/ml nicotine containing products non relevant in Europe for electronic cigarette, but relevant for pharmaceutical products</p>	See Table 1, answer 9.
568	Champagne ac Maxime,Phode,France	SCIENTIFIC OPINION	<p>p51 lines 39 to 42 "Of these, 39 solely a single study which evaluates the effects of regular passive smoking exposure due to 40 electronic cigarettes within the home, demonstrating increased levels of ambient air nicotine and biomarkers of nicotine (Ballbet al., 2014).</p> <p>The airborne markers were statistically higher in conventional cigarette homes than in e-cigarettes homes (5.7 times higher). However, concentrations of both biomarkers among non-smokers exposed to conventional cigarettes and e-cigarettes' vapour were statistically similar (only 2 and 1.4 times higher, respectively). The</p>	Please see the reply to comment 177.

569	Poirson Philippe,S ovape,Fran ce	SCIENTIFIC OPINION	<p>levels of airborne nicotine and cotinine concentrations in the homes with e-cigarette users were higher than control homes (differences statistically significant). Our results show that non-smokers passively exposed to e-cigarettes absorb nicotine. This study was realised at home thus It is important to take in count other source of nicotine contamination within the home as e-cigarette user are very often former smokers ie third hand tobacco smoke https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230406/</p> <p>[p.12 l. 1-2] The self-titration effect in nicotine users is well known and established. It is necessary to clarify it so that the reader understands the context of the topic of nicotine delivery.</p> <p>[p. 12 l. 42-45] Absence of toxic such as carbon monoxide, and the enormous reduction of carbonyl and PaH emissions in the aerosol of vaping compared to cigarette smoke are documented data (Shahab 2017, Dusautoir 2021) and relevant to assess the impact of TPD on the public, in the context where more than 98% of vaping users are or have been smokers.</p> <p>[p. 13 l. 5-9] The Public Health England (2015-2020) and Royal College of Physicians (UK) (2016) have conducted comprehensive assessments of the scientific evidence to evaluate a reduction of at least 95% of the risk of vaping versus smoking. These evaluations should be made known to the reader.</p> <p>[p. 13 l. 19] Actual TPD is limiting nicotine levels to 20 mg/ ml. It is important to point out to the reader that the risk of poisoning with more concentrated liquid increases in countries with regulatory restrictions forcing users to obtain supplies from alternative sources.</p> <p>[p. 13 l. 40] This should be corrected to specify that these literature data are for smoking, which releases nearly 7000 toxic substances. They cannot be applied to vaping.</p> <p>[p. 14 l. 52] To be relevant to the subject of the report, i.e. TPD, studies and data on products not authorised for sale in the EU should mentioned as illegal in EU or not be taken into account. As mentioned p. 9 l. 7-9, some substances are banned by TPD. Must</p>	<p>Please see the details in the chapter on Rationale.</p> <p>See Table 1, answer 1.</p> <p>See Table 1, answer 1.</p> <p>See table 1 comment 9.</p> <p>The (RAPEX) Safety Gate rapid alert system enables quick exchange of information between EU/EEA member states, the UK and the European Commission about dangerous non-food products posing a risk to health and safety of consumers e.g. for non-compliance with legal requirements.</p>
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be corrected systematically.

[p. 15 l. 7] It is necessary to clarify that the effect of elevated blood pressure is a temporary phenomenon in acute settings for the reader to understand the scope of the evidence evaluated.

Please see the details in the chapter on Rationale.

[p. 15 l. 19-34] + [p. 16 l. 21-25] The report must specify or exclude data on products that are not authorised on the European market. The nicotine used in legal liquids in EU is a pharmaceutical grade, with only traces of nitrosamines (similar to gums or patches). Several other substances presented here seem to come from studies on liquids outside Europe.

See Table 1, answer 4.

[p. 17 l.13] The well-known reactance responsiveness of young people to stigmatising campaigns, such as those in the USA (Aronofsky 2018), should be mentioned and taken into account in risk factors to encourage use vaping by young.

The comment is not clear.

[p. 17 l. 20 ss.] The US studies mentioned did not take into account the predominant cofactor of smoking by relatives and friends, suffer from high attrition, etc. These studies have quality defects from serious to critical according to Chan et al. 2020.

See Table 1, answers 5, 6, 7 and 8.

Chyderiotis 2020, a French study from OFDT, must be taken into account by the SCHEER although it is much more scientifically robust and concerns a situation in the context of TPD.

See Table 1, answer 2.

Reliable data do not support the gateway hypothesis with the scientific criteria of a causal relationship. In particular, youth smoking rates have dropped sharply since the appearance of vaping, which is inconsistent with this hypothesis. Other criteria are not met (Etter 2018). This whole chapter needs to be completely revised.

See Table 1, answer 5.

[p. 18 l. 23] The data on the market share in the USA is unsourced, erroneous and irrelevant. Also cited in (p. 65 l. 12) come from Nielsen, who specify that only concern sales in the retail channel, without taking into account sales in specialised vape shops and online.

The Opinion was adapted.

			[p. 18 35-39] This is a subjective opinion with no scientific basis in the European context, whose data shows the opposite of what is affirmed by the SCHEER.	See Table 1, answer 5.
			[p. 18 41] Many data were not taken into account by SCHEER on this issue. Millions of Europeans who have quit smoking with vaping will not understand this conclusion.	See Table 1, answer 6.
570	christian sottilotta,private,Italy	SCIENTIFIC OPINION	the electronic cigarette is really low risk	Thank you for your comment.
571	Gallus Silvano,Istituto di Ricerche Farmacologiche Mario Negri IRCCS,Italy	SCIENTIFIC OPINION	Chapter 3.1 - Page 13, lines 11-13: Although I agree that the analysis of the effects/intoxications of counterfeit products is out of the scope of the present report, it could be important to mention that, given the relatively large proportion of counterfeit conventional cigarettes we observed in the past decades, it is very likely to expect a huge production of counterfeit liquids that might have a value of several hundred euro per litre.	See Section 6.1, last paragraph.
572	Becher Rune,Norwegian Institute of Public Health,Norway	SCIENTIFIC OPINION	The preliminary opinion has mainly been based on review articles. This is useful for summarizing an area relatively quickly and especially where overviews are available for all the most important areas. It is a pragmatic approach to a field of knowledge with a large number of publications. However, this results in an opinion based on second-hand information. It may also divert attention from questions that are not covered in review articles.	The SCHEER used these reviews and meta-analyses critically and supplemented it with pertinent literature.
573	No agreement to disclose personal data	SCIENTIFIC OPINION	P11 L23 ACCIDENTAL POISONING IS ADDRESSED THROUGH THE EUTPD MEASURES The Opinion fails to evaluate and consider the effectiveness of these measures pre-and post-EUTPD implementation in Member States. P12 L29THERE IS NO EVIDENCE THAT “SECOND-HAND EXPOSURE” TO EXHALED E-CIGARETTE AEROSOLS IS A RISK TO BYSTANDERS BASED ON CURRENT SCIENCE IN MULTIPLE COUNTRIES We have provided a number of scientific studies that were absent in the Opinion and should be considered.[1]	This question was not part of the mandate. Please read our conclusion carefully.

P13 L6 THE WHO STATED E-CIGARETTES COULD REPRESENT “A SIGNIFICANT PUBLIC HEALTH ACHIEVEMENT”

See Table 1, answer 1.

In canvassing selective WHO’s views on e-cigarettes, SCHEER omits that, in 2016, WHO also stated: “If the great majority of tobacco smokers who are unable or unwilling to quit would switch without delay to using an alternative source of nicotine with lower health risk, and eventually stop using it, this would represent a significant contemporary public health achievement” [2].

P13 L38 HEALTH RISKS AND BENEFITS OF E-CIGARETTES ARE NOT CONSIDERED IN THE CONTEXT OF ADULT SMOKERS TRANSITIONING - EITHER PARTIALLY OR EXCLUSIVELY - TO E-CIGARETTES

See Table 1, answer 1.

The Opinion focuses exclusively on the absolute risk of e-cigarettes with no consideration to the relative risk of e-cigarettes compared to combustible tobacco cigarettes and their potential for tobacco harm reduction amongst current adult smokers. The Opinion also doesn’t present its conclusions in appropriate context: it fails to acknowledge the limitations of studies and their associated methodologies it cites.

P17 L18 REAL-WORLD DATA AND THE SCIENTIFIC EVIDENCE BASE DO NOT SUPPORT THE ‘GATEWAY THEORY’

See Table 1, answer 5.

Despite some e-cigarette experimentation amongst never-smokers in different countries, regular use of e-cigarettes by people who have never smoked is extremely rare. In particular, experimentation amongst adolescents is often misconstrued in research and subsequent media headlines with no understanding of previous smoking history documented. It is important to understand the nuances in reported behaviour (one-off experimentation and one-off use in a 30-day period versus regular weekly or daily use). E-cigarette trends must continue to be closely monitored and youth access prevention should remain a top priority for all manufacturers and governments, but SCHEER presents no evidence in its opinion that e-cigarettes are a gateway product to smoking combustible tobacco in any Member State. In the UK, where the EUTPD was

transposed into national legislation and frequent monitoring is conducted, it was shown in 2019 that, amongst 11-18 year old who also smoked, regular use (at least once a week) of e-cigarettes remained very low at 1.7% [3]. Amongst never smokers, regular use of e-cigarettes was 0.2% with youth smoking rates at an all-time low.

P18 L22 OPEN-SYSTEM PRODUCTS CAN MORE EASILY BE TAMPERED AND ADULTERATED BY USERS SCHEER fails to differentiate between closed and open systems. Open system devices, which allow for any liquid (incl. DIY and EU-unnotified liquids) to be used, can be customized mechanically by users to increase power, which increases nicotine yields. Scientific studies have shown[4] that variable and increased voltage open system products can deliver increased nicotine concentrations and are able to exceed the nicotine delivery profiles of tobacco cigarettes, even when using low nicotine strength liquids. Thus, open system e-cigarettes may have implications for abuse liability and should be closely monitored by EU regulators and the data stratified in the Opinion according to device type used in the cited studies.

P18 L36 IN THE UK, A COUNTRY THAT HAS EMBRACED TOBACCO HARM REDUCTION VIA E-CIGARETTES, SMOKING RATES ARE NOW THE SECOND LOWEST IN EUROPE AND DECLINES IN YOUTH SMOKING ARE THE LARGEST ON RECORD



Scientific_opinion.pdf

Different types of e-cigarettes are discussed in Section 6.1 and 6.2. However, the risk assessment relies on the available measured data in aerosols generated. In this approach maximum average concentrations are used for the calculation of the MoE.

Please see Table 1, answer 1.

574 Chaplia Maria,Con sumer Choice Center,Uni ted States SCIENTIFIC OPINION

PAGE 13, LINES 5-9: Public Health England established already in 2015 that vaping is 95% less harmful - and confirmed in 2020 that vaping has a small fraction of the risks of smoking. The same conclusion has been drawn by the New Zealand Ministry of Health and Health Canada, which have both launched public initiatives imploring smokers to turn to vaping. Vaping was endorsed by Joachim Schüz, head of environment and radiation at the WHO's cancer research agency, the International Agency for Research on

See Table 1, answer 1.

Cancer during his speech at The Committee on the Environment, Public Health and Food Safety of the European Parliament in February 2020. In his opinion, e-cigarettes are in “no way as harmful” as tobacco cigarettes and could help heavy smokers to quit.

PAGE 13, LINES 36-38: No one argues that there are no health risks at all. However, the risks associated with vaping have to be compared with those related to conventional smoking. Also, it is established that the risk of cancer from e-cigarettes compared to that from smoking is less than half a per cent. Therefore, vaping is an important tool to improve public health.

See Table 1, answer 1.

PAGE 18, LINES 35-39: The main drive behind proposed flavour bans is protecting minors, who are allegedly drawn to the myriad of vape flavours. But considering all minors who use these products are acquiring them outside the legal market, it is clear that the most immediate impact will be on responsible adult vapers who prefer these flavours.

This is outside the scope of the mandate of SCHEER

The latest CDC in the US figures show that 20.8% of high schoolers have vaped at least once in the last 30 days. But nearly half of those 7 were vaping cannabis rather than nicotine, usually products that were procured illegally.

This is outside the scope of the TPD

As already mentioned, only 2,1% of non-smoking individuals surveyed frequently used e-cigarettes. The data from Action on Smoking and Health (ASH) UK reports similar findings and states that youth smoking rates are at an all-time low and youth use of e-cigarettes is rare and most users are current or former smokers.

See Table 1, answer 5.

Page 19, Lines 1-7: Adults who use vaping and e-cigarettes as a means to quit smoking are vastly improving their chances of living long, healthy, and productive lives because by choosing vaping they get an opportunity to switch. One study found that the increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level. Another study, led by the Queen Mary University of London Professor Peter Hajek found that vapour products are

See Table 1, answer 6.

almost twice as effective for smoking cessation than nicotine-replacement therapy.

Ref:

Zhu (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population survey

Press release (2018). Action on Smoking and Health, New ASH data reveals that youth use of e-cigarettes in Great Britain is very low

Website of Government of Canada: Vaping and quitting smoking

Stephens (2017). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke

Nora's blog NIH. Monitoring the Future Survey Results Show Alarming Rise in Teen Vaping

Hajek (2019). A randomised trial of e-cigarettes versus nicotine replacement therapy FDA Press release. Results from 2018 National Youth Tobacco Survey show dramatic increase in e-cigarette use among youth over past year

Ministry of Health, New Zealand, Supporting smokers to switch to significantly less harmful alternatives

McNeill (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020. A report commissioned by Public Health England

575 Wyszynska-Szulc Agnieszka, Philip Morris Products S.A., Switzerland

SCIENTIFIC OPINION

P. 13 l. 1. 36-48
The SCHEER's Opinion omits the health effects of switching from smoking to e-cigarettes. This omission neglects the body of evidence reporting reduction in respiratory symptoms in those switching. We suggest adding the concept of relative risk throughout the whole paragraph.

See Table 1, answer 1.

P. 13 l. 45 - 48 we recommend referring to cardiovascular effects as "acute" effects, due to the lack of long term data.

The Opinion has been adapted.

P. 15 l. 5-6
The conclusion made later in the SCHEER's Opinion: "The health impacts of electronic cigarette's use are still difficult to establish due to the lack of long-term data from epidemiological studies or clinical trials" does not substantiate that the weight of evidence for risk of long-term systemic effects on the cardiovascular system is "strong".

The Opinion has been adapted.

P. 18 l. 1-7
Public Health England (McNeill 2020) raises valid concerns smokers/vapers have in relation to potential flavour bans. We suggest to add on p. 18, l.6 their advice that "a ban on flavoured liquids could have the adverse effects and unintended consequences

This is risk management and is outside of the mandate of SCHEER

for smokers using vaping products to quit. It should only be considered with caution.” We suggest to add on p.18, l.7 the findings from Romijnders (2019) and Leventhal (2019) on the need for a balanced approach to regulation of flavours.

P.18 1. 30-33
We suggest to delete “Health effects of electronic cigarette use are mainly due to nicotine (...)”. According to COT, US FDA, and many others nicotine is addictive and not risk-free, but is not the main cause of smoking-related diseases. Nor is it considered as carcinogenic, cardiovascular or respiratory toxicant according to the US FDA (2012). Diseases, such as lung cancer, cardiovascular disease and emphysema, are caused primarily by inhaling harmful compounds formed when tobacco is burned.

The Opinion has been revised.

P. 18 1. 35-36
The SCHEER’s Opinion omits several studies from EU that dismiss the gateway hypothesis. E.g., data from Chyderiotis (2020) show that adolescents in France who have tried e-cigarettes are less likely to later transition to daily smoking than those who had not; data from Italy (Gorini 2020) indicate that e-cigarettes do not seem to have caused an increase in tobacco smoking between 2010 and 2018; a survey from Greece (Soteriades 2020) concluding that “it seems that e-cigarette use may contribute to a net reduction in the use of combustible tobacco products among adolescent students”. Also McNeill (2015) and Etter (2018) question the gateway effect. Therefore, we believe that there is no substantiation for calling the evidence “strong” (p. 18, l. 35), in particular for Europe. We suggest to change the conclusions in line with the latest evidence, relevant for Europe, which we reference in our response.

Please see Table 1, answer 5.

P. 18 1. 41-55, P. 19 1. 1-7
The SCHEER’s Opinion omits several recent studies demonstrating the effectiveness of e-cigarettes in smoking cessation. Consideration of the studies cited in our comment to Section 6.7 would influence the SCHEER’s determination that “evidence for smoking cessation is weak and for smoking reduction it is weak to moderate” on p.19 l. 1-2. We suggest adapting the conclusions on p. 18 l.44-55 and p.19 l. 1-7 according to the most recent evidence

Please see Table 1, answer 6.

which demonstrates the effectiveness of e-cigarettes in smoking cessation.

The role of flavours in helping smokers switch has been omitted. We therefore suggest the following be added to p.19 l. 8: “Several studies demonstrate that non-tobacco flavoured and non-menthol flavoured, especially fruit flavoured e-liquids, facilitate the switching of smokers compared to traditional tobacco and menthol flavoured e-cigarettes (Romijnders (2019); Du (2020) & Russel (2018), Gravely (2020), Friedman (2020) & Havermans (2019)).”



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576 O'Leary Renee, Center of Excellence for the Acceleration of Harm Reduction, University of Catania, Italy, Italy	SCIENTIFIC OPINION	<p>P12L37-38 Second-hand exposure levels should be evaluated against known occupational exposure standards.</p> <p>P12L42 The Opinion does not address the use of non-nicotine liquids. For EU youth 42% - 52% and more use non-nicotine liquids, and 30% - 60% of EU adults use non-nicotine liquids. See data in section 6.5.1.</p> <p>P13L34 Consumer education on the safe use of lithium ion batteries could reduce the risk of injury with ENDS and in addition for other lithium ion battery powered devices.</p> <p>P15L5-6,12-14, P13L47 The National Academies of Sciences, Engineering, and Medicine systematic review that states “Conclusion 9-1. There is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification) (p. 7). Four additional reviews support the NASEM conclusion. See section 6.5.4. The Opinion statement should be revised.</p> <p>P16L42 The EU prevalence of adult ENDS users is far lower than for cigarettes, with 8 countries between 4.1% and 5.7% and 13 countries under 2%. The prevalence of ENDS use has been relatively stable from 2017 to 2019. Only two countries had the</p>	<p>The SCHEER based the conclusions on published risk assessments. Occupational standards are a subset of standards that may be used.</p> <p>This is outside the scope of the TPD.</p> <p>Thank you, but this is outside the scope of this Opinion.</p>
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prevalence rate of adult ENDS users rise by 1%. Seven countries had an increase of only 0.2% or less, and 3 countries had no increase. See EUROMONITOR Data file.

P16 Section 2 The Opinion frequently cites ever-use data as evidence. Ever-use is a problematic measurement that captures a substantial number of one-time triers and can result in bias in findings. The Global Youth Tobacco Survey reported that 27% - 55% of EU youth used ENDS only once. The EUREST-PLUS ITC found that over 60% of EU adult ever users had tried ENDS 10 times or less. See section 6.5.1. The seven of nine statements in this section based on ever-use should be interpreted with caution.

P17L3-13, P17L36-38. The most common reason by far for youth ENDS experimentation is curiosity, not flavours. See data in section 6.6.

P17L20-27 The analysis by Shahab et al. (2020) “provides substantial evidence for the null hypothesis ie, that there is no gateway” (p. 5). The results of the Chyderiotis et al. study (2020) in France are “in contradiction with the gateway hypothesis” (p.5). See our comments on an alternative hypothesis in section 2.1 and additional evidence in section 6.6.

P18L3 A large US survey found no difference in youth ENDS users for smoking initiation from flavored or non-flavored ENDS use. Study in section 6.6.

P18L35-36 Based on the studies cited in section 6.6, the conclusion should be amended to read that there is “mixed evidence.”

P19L1-7 The recently published Cochrane review concludes there is moderate-certainty evidence that ENDS use for cessation result in a higher quit rate than NRT. US longitudinal studies show ENDS users have higher quit rates than non-users. See evidence in section 6.7

P21L51-53 More stringent ENDS regulation in the EU than in the U.S. was instrumental in preventing cases like EVALI, as

acknowledged by many experts in their answers to written questions by the Members of the European Parliament in 2019. While a high level of public health protection is taken into account by the European Directive (TPD) when regulating ENDS, it is crucial to improve capacities of the national authorities to enforce compliance by proper enforcement measures, increased utility of the tools offered by TPD (e.g. EU-CEG system for reporting) as well as closer enforcement cooperation between Member States. Further research is also needed to address the gaps in the scientific evidence as well as to better understand the health impacts of ENDS.

References:

Chyderiotis, S., Benmarhnia, T., Beck, F., Spilka, S., & Legleye, S. (2020). Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France?. *Drug and Alcohol Dependence*, 208, 107853.
 Shahab, L., Beard, E., & Brown, J. (2020). Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study. *Tobacco Control*. Advance Online Publication 13 January 2020

<p>577 Serafimov Lubomir, Bulgarian Vape Association of Manufacturers, Importers and Distributors of Electronic cigarettes and Nicotine and Nicotine free E-liquid, Bulgaria</p>	<p>SCIENTIFIC OPINION</p>	<p>We find the Opinion lacking of adequate comparison with traditional tobacco cigarettes and other benchmarks. Electronic cigarettes are primarily used as alternatives to smoking and their health impact when used as substitute for cigarettes is highly beneficial, involving large decreases in exposures to toxicants. With the huge percentage of EU citizens smoking (around 26%) and thus being exposed to most serious risks of disease and premature death, it is inexplicable that e-cigarette risks are not positioned in comparison to cigarettes. This essential information about relative risk is absent throughout the whole assessment.</p> <p>There is a huge body of evidence showing that e-cigarette users are exposed to significant in comparison to smoking cancer risk and there are also significant improvements in the cardiovascular system when smokers switch to e-cigarettes.</p> <p>In the case of explosions and fires, the relevant comparator is fires and related injuries caused by smoking materials – there is around three orders of magnitude difference. For example, according to the US National Fire Protection Association, around 18,000 fires were caused annually in the US by smoking materials from 2012-16. Yet the same association reported just 15 fires and explosions with e-</p>	<p>See Table 1, answer 1.</p> <p>Risk comparison was not within the scope of this Opinion.</p> <p>Thank you for this information.</p>
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cigarettes in 2015.

These relative risk findings are wholly absent from the SCHEER assessment.

There is no sign in the Opinion that SCHEER has placed the risks they discuss into a useful context by using other frameworks for assessing tolerability of risk, for example, occupational health exposures limits. Burstyn, 2013 made an early assessment of e-cigarette toxic exposures relative to ‘total limit values’ (TLV) for occupational health exposures.

These study findings are highly relevant to policymakers yet they are not provided in the SCHEER report.

References:

Burstyn, I. 2014 Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks.
 NFPA. Electronic Cigarette Explosions and Fires: The 2015 Experience
 NFPA. 2019. Home Fires Started by Smoking
 NFPA. 2019. Home Fires Started by Smoking. Supporting tables

See Section 6.5.5.4 and answer to comment 89. Standards can be useful in the evaluation of second-hand exposure.

578 Muntadas-Prim Ángeles,A NESVAP, Spain SCIENTIFIC OPINION Page 11. Lines 54-56 Comment See Table 1, answer 1.

Why does SCHEER make no reference to the chemical input of inhaling COMBUSTED TOBACCO SMOKE based on smokers with a 10-puff topography?

579 Muntadas-Prim Ángeles,A NESVAP, Spain SCIENTIFIC OPINION Page 12. Lines 1-5 Comment

Nicotine self-titration is key to avoid craving and maintain people smoke-free. It is the bio-mechanism that ensures vapers and smokers to not be poisoned while vaping or smoking. The SCHEER considers nicotine consumption as unacceptable for smokers and electronic cigarettes users while it is well accepted for NRTs even when administered in combination at high concentrations. The fact that e-cigarettes deliver a good amount of nicotine is a fundamental advance in the technology of these devices in order to be successful in smoking cessation. That is precisely the goal of electronic cigarettes. The same as with NRTs.

Ref:

Thank you for your comment.
 See Table 1, Answer 1. See also the assessment of risks from exposure to nicotine in Section 6.5.

			<p>Farsalinos K, Poulas K, Voudris V. Changes in Puffing Topography and Nicotine Consumption Depending on the Power Setting of Electronic Cigarettes. <i>Nicotine Tob Res.</i> 2018 Jul 9;20(8):993-997. doi: 10.1093/ntr/ntx219. PMID: 29059377. https://pubmed.ncbi.nlm.nih.gov/29059377/</p> <p>Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced ecigarette users: blood nicotine delivery and subjective effects. <i>Psychopharmacology (Berl)</i>. 2016 Aug;233(15-16):2933-41. doi: 10.1007/s00213-016-4338-2. Epub 2016 May 27. PMID: 27235016. https://pubmed.ncbi.nlm.nih.gov/27235016/</p> <p>Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. <i>CNS Drugs</i>. 2001;15(6):453-67. doi: 10.2165/00023210-200115060-00004. PMID: 11524024. https://pubmed.ncbi.nlm.nih.gov/11524024/</p>	
580	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	<p>Page 12. Lines 7-17</p> <p>Comment The weight of evidence for determining the composition of tobacco smoke is well described, however, the SCHEER opinion makes no reference to that.</p>	See Table 1, answer 1.
581	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	<p>Page 12. Lines 19-40</p> <p>Comment There is no possible circumstance in which the particulate matter in the aerosol produced by e cigarettes is as solid and toxic as it is in tobacco smoke or even in the air of any city. The SCHEER talks about particulate matter, nicotine, glycerol, propylene glycol, formaldehyde and acetaldehyde, volatile organic compounds (VOCs), metals and polycyclic aromatic hydrocarbons. Things we all breathe as normal, including nicotine, and the much more dangerous particulate matter derived from combustion engines, which is a standard marker for any urban atmosphere. The SCHEER compares inhaled aerosol with exhaled aerosol instead of comparing exhaled aerosol with tobacco smoke (first and secondary stream). The SCHEER ensures the data is inconsistent, but they do not compare the aerosol of e cigarettes with the air quality of many streets (in any standard city) which all citizens continuously breathe.</p> <p>References van Drooge BL, Marco E, Perez N, Grimalt JO. Influence of electronic cigarette vaping on the composition of indoor organic pollutants, particles, and exhaled breath of bystanders. <i>Environ Sci Pollut Res Int</i>. 2019 Feb;26(5):4654-4666. doi: 10.1007/s11356-018-3975-x. Epub 2018 Dec 18. PMID: 30560536. https://pubmed.ncbi.nlm.nih.gov/30560536/</p> <p>Esther Marco and Joan O.Grimalt. A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic</p>	See Table 1, answer 1. Additionally: the continuous breathing exposure scenario is not applicable to the exposure scenario for e-cigarette users as explained in section 6.5.5.2.

cigarette smokers. Institute of Environmental Assessment and Water Research (ID/EA), Spanish Council for Scientific Research (CSIC), 2015. <https://www.sciencedirect.com/science/article/abs/pii/S0021967315010821>

Daniel Martín, Miguel Peñín-Ibáñez, Alicia González González, María Jesús Santos-Delgado, Angel González Ureña. On the Passive Exposure to Nicotine from Traditional Cigarettes Versus e-Cigarettes. Open Science. March 2019, Vol 7 No 1 Pages 11-17. <http://www.openscienceonline.com/journal/archive2?journalId=718&paperId=4979>

Renée O’Leary, PhD(c) Marjorie MacDonald, PhD, RN Tim Stockwell, PhD Dan Reist, MTh. Clearing the Air: A systematic review on the harms and benefits of e-cigarettes and vapour devices. University of Victoria. Centre for Addictions Research of BC (CANADA). 2017 <https://www.uvic.ca/research/centres/cisur/assets/docs/report-clearing-the-air-review-execsummary.pdf>

Burstyn, I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. BMC Public Health 14, 18 (2014). <https://bmcpublihealth.biomedcentral.com/articles/10.1186/1471-2458-14-18>

582	Muntadas-Prim	SCIENITIC OPINION	Page	12.	Lines	42-47
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Comment
 The MINOR cardiovascular effects produced by nicotine are well known, however they are not associated with MAJOR cardiovascular affairs. Long-term inhalation of nicotine was tested in animals in Waldhum et al 1996 and no adverse effects on the lungs or development of atherosclerosis were observed. The greatest source of CV risk in tobacco is not nicotine but CO, which is not present in e cigarettes. E cigarettes are a harm reduction tool, not a harmless tool. Typically, similar concentrations of nicotine have been found in NRT users, many of whom have used these products for many years, even for a lifetime; but this does not seem to be a problem for the SCHEER.



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The Opinion has been revised accordingly regarding the health effects of electronic cigaretees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

583	Muntadas-Prim	SCIENITIC OPINION	Pages	12-13.	Lines	47-3
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Comment
 More information is needed on the inhaled risks of flavours, but they’ve been monitored since 2016 and there has been no important issue to date; plus the vast majority of flavouring compounds in e-

The SCHEER agrees.

cigarette liquids are present at far lower levels than required to classify them as toxic. Again, the SCHEER does not make any reference to the toxicity of tobacco smoke compared to the theoretically toxicity of flavours.

See Table 1, answer 1.

Ref.:
 Farsalinos K, Lagoumintzis G. Toxicity classification of e-cigarette flavouring compounds based on European Union regulation: analysis of findings from a recent study. *Harm Reduct J.* 2019 Jul 25;16(1):48. doi: 10.1186/s12954-019-0318-2. PMID: 31345235; PMCID: PMC6659232. <https://pubmed.ncbi.nlm.nih.gov/31345235/>

584	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	Page 13.	Lines	15-17	Thank you for this suggestion. However, the SCHEER uses the literature published and cannot do research herself.
<p>Comment The SCHEER should review literature on the hygroscopic nature of PG and its drying effect of the mucous membranes, which, in fact, doesn't have any clinical significance (drinking water is a good solution). As consumers, we respectfully ask SCHEER to further document themselves by interviewing vapers regarding their experience while vaping.</p>						
<p>Ref: Werley MS, McDonald P, Lilly P, Kirkpatrick D, Wallery J, Byron P, Venitz J. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. <i>Toxicology.</i> 2011 Sep 5;287(1-3):76-90. doi:10.1016/j.tox.2011.05.015. Epub 2011 Jun 12. PMID: 21683116. https://pubmed.ncbi.nlm.nih.gov/21683116/ ROBERTSON OH, LOOSLI CG, et al. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. <i>J Pharmacol Exp Ther.</i> 1947 Sep;91(1):52-76. PMID: 20265820. https://pubmed.ncbi.nlm.nih.gov/20265820/ Corcoran TE, Niven R, Verret W, Dilly S, Johnson BA. Lung deposition and pharmacokinetics of nebulized cyclosporine in lung transplant patients. <i>J Aerosol Med Pulm Drug Deliv.</i> 2014 Jun;27(3):178-84. doi: 10.1089/jamp.2013.1042. Epub 2013 May 13. PMID: 23668548; PMCID: PMC4088352. https://pubmed.ncbi.nlm.nih.gov/23668548/ ROBERTSON OH. Disinfection of air by germicidal vapors and mists. <i>Am J Public Health Nations Health.</i> 1946 Apr;36:390. PMID: 21020083. http://www.e-cig.org/pdfs/1946-Synopsis-On-PG-As-Disinfection-Vapor.pdf OH Robertson. Disinfection of Air by Germicidal Vapors and Mists. Referee's report to the STANDARD METHODS COMMITTEE FOR THE EXAMINATION OF GERMICIDES AND ANTIBACTERIAL AGENTS. Committee authorized 1941. Published Reports, A.I.P.H., May, 1943, Aug., 1944, and Aug., 1945. https://pubmed.ncbi.nlm.nih.gov/21020083/</p>						
585	Muntadas-Prim	SCIENTIFIC OPINION	Page 13. Comment	Lines	20-24	Thank you for your comment. No change needed.

	Ángeles,A NESVAP, Spain		Child-proof packaging has been working well in the EU since 2016 (and even before). Many dangerous products that we all have and use at home do not come in child resistant packaging. The lethal dose of nicotine has been seriously and elaborately discussed. Ref.: Lambert H, Manel J, Gabrion I. Intoxications par les produits domestiques [Poisoning by household products]. Rev Prat. 2000 Feb 15;50(4):365-71. French. PMID: 10748666. https://pubmed.ncbi.nlm.nih.gov/10748666/ Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88(1):5-7. doi:10.1007/s00204-013-1127-0 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/		
586	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	Page Comment 13. Could the SCHEER PLEASE name the studies on which they have relied to reach that conclusion?	Lines 45-48	The Opinion is the conclusion of the scientific rationale. Please check the Rationale (Chapter 6) for supporting references.
587	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	Page Comment 13. Could the SCHEER compare them with the risk of continuing to smoke?	Lines 36-38	See Table 1, answer 1.
588	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	Page Comment 14. Could the SCHEER provide a useful approach to regulators? For example, handing over an estimated comparative of the input of formaldehyde, acrolein and diacetyl in tobacco smoke vs e cigarette aerosol would be interesting. In fact, diacetyl was eliminated from e liquids years ago. The vast majority of e liquids in the EU do not contain diacetyl. Formaldehyde depends on the correct use of the device and it is extremely easy for the consumer to detect its presence because of its horrible taste. Wouldn't the consumers be expected to use the devices correctly? How many daily life practices also produce exposure to several concentrations of formaldehyde and acrolein?	Lines 52-55.	Risk management is outside the mandate of the SCHEER. For measured exposures: see Section 6.5.2



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589	Muntadas-Prim Ángeles,A NESVAP, Spain	SCIENTIFIC OPINION	<p>Page 15. Lines 19-34.</p> <p>Comment This is a product addressed to smokers. There is clear scientific evidence stating that the carcinogenic risks are astonishingly much lower than smoking.</p> <p>Ref: Stephens WEComparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tobacco Control 2018;27:10-17. https://tobaccocontrol.bmj.com/content/27/1/10 Maciej L. Goniewicz , Benjamin C. Blount , Jamie Brown et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users. https://www.acpjournals.org/doi/10.7326/M16-1107 Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Ann Intern Med. 2017 Mar 21;166(6):390-400. doi: 10.7326/M16-1107. Epub 2017 Feb 7. PMID: 28166548; PMCID: PMC5362067. https://pubmed.ncbi.nlm.nih.gov/28166548/</p>	See Table 1, answer 1.
590	Kuna Piotr,Medi cal University of Lodz, Poland,Pol and	SCIENTIFIC OPINION	<p>General comments to the scientific opinion. In Poland we have currently almost 10 000 (ten thousand) different liquids for open system e-cigaretes officially available. There is no data what they contain, what is the harm, what contains aerosol derived after heating the liquid. Base on the literature review only close systems contains well know ingredients and analysis of delivered aerosol after heating the liquid should be accepted. Another words closed-controlled- well defined systems. In the literature such a cigarettes have a better efficacy in regular cigarets quitting than nicotine patch. Attached supportive literature.</p> <p>Ref: George (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes Hajek (2019). A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy Biondi (2020). Electronic cigarette Hartmann-Boyce (2020). Electronic cigarettes for smoking cessation. Cochrane Review Abrams (2018). Harm Minimization and Tobacco Control- Reframing Societal Views of Nicotine Use</p>	See Table 1, answer 1.
591	Ribes Arturo,UP EV,Spain	SCIENTIFIC OPINION	<p>Page 13. Lines 20-24.</p> <p>Comment: Child-proof packaging has been established by EU tobacco products directive and is working without any problems identified in the EU. The consumers directorate of the European Commission has not received any concerns on this regard in all this time. It is regrettable that the SCHEER points at this aspect as if it</p>	In the view of the SCHEER, the sentence pointed out is neutral and does not present this as an issue or problem.

were an issue or a problem when the packaging of this products is well regulated.

Ref:

Lambert H, Manel J, Gabrion I. Intoxications par les produits domestiques [Poisoning by household products]. Rev Prat. 2000 Feb 15;50(4):365-71. French. PMID: 10748666. <https://pubmed.ncbi.nlm.nih.gov/10748666/>

Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88(1):57. doi:10.1007/s00204-013-1127-0

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/>

592 Ribes Arturo,UP EV,Spain SCIENTIFIC OPINION Page 15. Lines 19-34. See Table 1, answer 1.

Comment This is a product addressed to smokers. Scientific evidence and research show the vast difference between carcinogenic risks for vaping and smoking.

Ref:

Stephens WEComparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smokeTobacco Control 2018;27:10-17. <https://tobaccocontrol.bmj.com/content/27/1/10>

Maciej L. Goniewicz , Benjamin C. Blount , Jamie Brown et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users. <https://www.acpjournals.org/doi/10.7326/M16-1107>

Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. Ann Intern Med. 2017 Mar 21;166(6):390-400. doi: 10.7326/M16-1107. Epub 2017 Feb 7.

PMID: 28166548; PMCID: PMC5362067. <https://pubmed.ncbi.nlm.nih.gov/28166548/>

593 Ribes Arturo,UP EV,Spain SCIENTIFIC OPINION Page 14. Lines 52-55. See answer to comment 588.

Comment: As representative of manufacturers, we can safely guarantee that diacetyl is not contained in e-liquids and that Foraledhyde only takes place when the product is misused or tampered against the specific recommendations of the manufacturer. Therefore, it is not contained in European products.

594 IKONOMI DIS IGNATIO S, National and Kapodistri an University SCIENTIFIC OPINION PAGE 15 LINES 5-6

According to the newly published data between 2018 -2020: (Ikonomidis et al Electronic cigarette smoking increases arterial stiffness and oxidative Stress to a lesser extent than a single conventional cigarette: an acute and chronic study. Circulation 2018;137:303–306.

Biondi-Zoccai G et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: the Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 randomized trial. J Am Heart Assoc 2019;8:e010455, George Jet al. Cardiovascular effects of switching from tobacco cigarettes

The Opinion has been revised accordingly regarding the health effects of electronic cigarettees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

of Athens
Greece

to electronic cigarette. *J Am Coll Cardiol* 2019;74:3112–3120. Kacey P et al. Differential effects of tobacco cigarettes and electronic cigarettes on endothelial function in healthy young people. *American Journal of Physiology-Heart and Circulatory Physiology* 2020 319:3, H547-H556, Ikonomidis I et al. Effects of electronic cigarette on platelet and vascular function after four months of use. *Food Chem Toxicol.* 2020 Jul;141:111389. doi: 10.1016/j.fct.2020.111389. Epub 2020 Apr 25. PMID: 32343994, Kelesidis T et al. Elevated Cellular Oxidative Stress in Circulating Immune Cells in Otherwise Healthy Young People Who Use Electronic Cigarettes in a Cross-Sectional Single-Center Study: Implications for Future Cardiovascular Risk. *J Am HAssoc.* 2020 Sep 15;9(18))

we would suggest to modify the sentence in page 15 lines 5,6 “The overall weight of evidence for risk of long-term systemic effects on the cardiovascular system is strong” to “The overall weight of evidence for risk of long-term systemic effects on the cardiovascular system is moderate” and to include in the following list of evidence the sentence “Compared to combustible tobacco products, the mid-term effects electronic cigarettes on surrogate markers of cardiovascular function appear to be less evident”

Comments on the summary on e-cigarettes for the Scientific Committee on Health Environmental and Emerging Risks (SCHEER)

This is a thorough summary on the health effects of electronic cigarettes that reviewed the most recent scientific information on behalf of the Scientific Committee on Health Environmental and Emerging Risks (SCHEER).

The various pathophysiological pathways, through which electronic cigarettes may affect cardiovascular health, either acutely or after chronic use, are evident in this statement paper. The studies included conclude that e-cigarette use enhances oxidative stress, endothelial dysfunction, and vascular injury and therefore may induce negative cardiovascular effects through these mechanisms.

Although there is a broad range of evidence for the adverse acute effects of e-cigarettes and their toxic properties on the cardiovascular system including oxidative stress and endothelial dysfunction, studies concerning the mid-term and long-term use of e-cigarettes and CVD risk are limited and controversial.

In a recent study Ikonomidis et al , investigated the effects of e-cigarette use on aortic stiffness as assessed by pulse wave velocity and augmentation index, exhaled carbon monoxide (CO) concentration, and oxidative stress as assessed by malondialdehyde plasma concentrations, both acutely and after 1 month of use compared to combustible tobacco use in 70

individuals. In this study, we have shown that both conventional cigarettes and e-cigarettes impair arterial elasticity and increase oxidative stress burden acutely. However, both nicotine-free and nicotine e-cigarettes resulted in a smaller increase in arterial stiffness and oxidative stress as compared to acute conventional cigarette smoking. Moreover, switching from conventional cigarettes to nicotine-containing e-cigarettes resulted in a reduction of central and brachial systolic blood pressure, arterial wave reflections, and oxidative stress within 1 month. This beneficial effect may be attributed to the observed large reduction in inhaled CO, which is produced by the combustible cigarettes but not by e-cigarettes.

These findings were also confirmed by a subsequent study by Biondi-Zoccai et al. who also found a smaller increase in oxidative stress markers after acute e-cigarette smoking compared to conventional tobacco smoking.

Similar findings have been published by George et al. in 114 smokers who were randomized to e-cigarettes with nicotine or e-cigarettes without nicotine for 1 month. In this study, vascular function was assessed by flow-mediated dilation of the brachial artery and pulse wave velocity. Within 1 month of switching from conventional cigarettes to e-cigarettes, there was a significant improvement in endothelial function and arterial stiffness with the largest improvement seen in women and those who complied best with e-cigarette switch. Indeed, those who complied best and avoided dual use had the lowest CO levels and benefitted the most in terms of improvement in endothelial function. Individuals with CO measurements within the lowest tertile had the greatest gain in vascular function improvement.

Another recent study in healthy subjects evaluated the effects of acute and chronic tobacco cigarette (TC) smoking and electronic cigarette (EC) vaping on FMD. FMD was significantly impaired after smoking one TC, but not after vaping an equivalent “dose” (estimated by change in plasma nicotine) of an EC.

Most recently Ikonomidis et al, examined the effects of electronic cigarette on platelet and vascular function after 4 months of use compared to tobacco smoking. Forty smokers without cardiovascular disease were randomized to smoke either conventional cigarettes or an electronic cigarette. After 4 months, continuation of conventional cigarette smoking further impaired platelet function compared to vaping as assessed by Platelet Function Analyzer PFA-100 and Light Transmission Aggregometry, (decline 24.1 vs 9.4%, respectively). Conversely, compared to smoking, vaping resulted in greater reduction of exhaled CO, improvement of PWV and reduction of MDA, a biomarker of oxidative stress.

Recently Kelesidis et al published a study evaluating cellular oxidative stress (COS) in circulating immune cells in healthy long-term EC vapers

compared with nonsmokers. An increased proportion of innate and adaptive immune cell subtypes has been found in long-term EC vapers and this is in concordance with the finding that they had elevated COS as well. The cellular oxidative stress was lower in long-term EC vapers compared with TC smokers and the authors conclude that additional investigation is needed to clarify whether switching to ECs as part of a harm-reduction strategy for cardiovascular disease is effective.

We do agree that future studies are needed to investigate both the long- and short-term effects of e-cigarette exposure on cardiovascular health—and particularly in the youth, as well as the effects of various types of e-liquids that contain flavors where data is scarce.

E-cigarettes, even though they are not completely harmless, could play a role as a harm-reduction strategy in long-term smokers of tobacco cigarettes that refuse or cannot quit smoking using the approved pharmacotherapy medication for smoking cessation.

Non-combusted nicotine as inhaled, transdermal and chewed or aerosolized NRT is well established as a smoking-cessation strategy. Cardiovascular effects of NRT have been studied in smokers and have not been associated with an increased risk of major cardiovascular adverse events. However, NRT are not risk free. Nicotine possesses sympathomimetic effects resulting to increased heart rate, myocardial contractility and vasoconstriction and thus, may cause myocardial ischemia and arrhythmias. However, we should take in account that the long term use of NRT is an approved method for smoking cessation.

Emissions from most e-cigarettes, like those from tobacco cigarettes, also contain nicotine but the plasma levels of nicotine rise slowly and peak at a lower level than combustible tobacco. In a meta-analysis of the autonomic cardiovascular effects of e-cigarette use, the acute increase in heart rate and blood pressure after e-cigarette vaping was significantly lower compared to tobacco cigarettes.

The danger of non-smoking adolescents taking on vaping and using nicotine-containing, flavored e-cigarettes is an new emerging public health problem as future adverse cardiovascular events are really unknown and e-cigarettes are certainly not risk free. Therefore, e-cigarettes should be marketed under strict laws and regulations (especially regarding youth population use) they should meet product standards and safety requirements, with full disclosure of all device and e liquid constituents, and constant premarketing and postmarketing testing.

According to the above newly published data between 2018 -2020, we would suggest to modify the sentence in page 15 lines 5,6 “The overall weight of evidence for risk of long-term systemic effects on the cardiovascular system is strong” to “The overall weight of evidence for

risk of long-term systemic effects on the cardiovascular system is moderate” and to include in the following list of evidence the sentence “Compared to combustible tobacco products, the mid-term effects electronic cigarettes on surrogate markers of cardiovascular function appear to be less evident”



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<p>595 Olteanu Vlad, Juul Labs Inc., Belgium</p>	<p>SCIENTIFIC OPINION</p>	<p>Overall, there is a problem with the general lack of justification used for the alignment between the assessment of the weight of evidence and the consistency of evidence. Overall in this section and throughout the document, definitions for the levels of assessment (strong, moderate, weak, uncertain, or not possible) are not provided.</p> <p>On the one hand (Page 12, lines 36-38), the weight of evidence for second-hand exposure assessment was judged to be ‘weak-to-moderate’ based on data, the consistency of which was judged to be ‘low’. On the other hand, (Page 15, lines 404-43), it was stated that the overall weight of evidence for risk for other long-term adverse health effects, such as pulmonary disease and CNS- and reprotoxic effects, cannot be established ‘due to lack of consistent data’.</p> <p>In both cases, the consistency of data was judged to be low but in one case, WOE is judged weak-to-moderate and in the other case, it ‘cannot be established due to lack of consistent data’.</p> <p>The definition of ‘moderate’ evidence (2018 NASEM - PDF is provided in our response to section 4) suggests that a general conclusion can be made, but limitations cannot be ruled out with reasonable confidence. However, if the SCHEER Opinion acknowledges a lack of consistent data, but rates the WOE as weak to moderate this implies a lack of objectivity in the report.</p> <p>Furthermore, in assessing the WOE and incidence of health concerns, the committee acknowledges that “The overall weight of</p>	<p>Reference is made to:SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Memorandum on weight of evidence and uncertainties, In this publication (to be found on the website of this Committee) you can find the justification requested.</p> <p>The overall weight of evidence is decided on the basis of consistency and quality criteria.</p> <p>See the Memortandum cited above.</p> <p>The weight-of-evidence determines the strength of the outcome of the assessment, which can be a low/high/medium risk.</p>
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evidence for risk of poisoning and injuries due to burns and explosion, is strong,” implying that there is consistency of data for reported incidents, but the discussion goes on to state that “However, the incidence is low. Therefore, the risk is expected to be low.” The report then dedicates a significant discussion to a risk that is acknowledged to be rare and modifiable. (pages 50-51, 52-53)

The length of any risk assessment is not always directly proportional to the degree of risk.

These discrepancies in the report are confusing and bias the overall assessment of the public health impacts (taking into account both risks and benefits) of e-cigarettes.

We suggest that the Opinion defines the terms of WOE and aligns the consistency of evidence and incidence of risk with the discussion.

Detailed critiques regarding scientific opinion are provided in subsequent sections.

596 Dahlmann SCIENTIFIC
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nb. Due to the 1mb/file limit we cannot upload full papers. We attach a document with the relevant web links. We hope SCHEER will understand and seek to review these links.

It is striking that throughout the report, the Committee fails to make any meaningful attempt to compare the risk of e-cigarette use to the risks of smoking. Given that, according to the Commission’s own data, less than 5% of e-cigarette users are never smokers, this would seem the obvious reference point when considering the risks associated with e-cigarette use.

See Table 1, answer 1.

The report should be reframed completely with reference to the risks of e-cigarettes as compared to the risks of smoking combustible cigarettes. A good example of how this can be done is Nutt et al (2014) , which systematically compares the risks of routine use of a wide range of nicotine containing products: “Cigarettes are the nicotine product causing by far the most harm to users and others in the world today. Attempts to switch to non-combusted sources of nicotine should be encouraged as the harms from these products are much lower.”

P13L19

SCHEER notes the risk of nicotine poisoning and later (p40) states that 60mg of nicotine is fatal for humans. This estimate was based on erroneous self-experiments performed in the mid of the 19th century and was been corrected to 0.5-1 g several years ago (Mayer, 2014).

The Opinion has been adapted.

P16L27

should be the main indicator of a “gateway effect”. Simply put, were vaping leading more young people to smoke, then we would see a higher prevalence of smoking among young people develop as the e-cigarette came to prominence.

See Table 1, answer 5.

However, in the past decade, smoking rates among youth have continuously decreased at unprecedented high rates in virtually all EU Member States. Data from the OECD shows that smoking among 15-16 year olds has fallen significantly in most EU countries between 2007 and 2015, the period in which e-cigarettes were introduced onto the EU market; and data from the German Government (attached) also shows a significant fall in youth smoking rates in that jurisdiction.

P18L41

The conclusion of the Committee does not take into account all of the available evidence. In addition to RCTs and cohort studies, survey data are important in measuring the effect of electronic cigarettes.

See Table 1, answer 6.

Farsalinos (2016) surveyed 27.460 EU citizens from the then 28 Member States. The study concluded that E-cigarette use in the European Union appears to be largely confined to current or former smokers, while current use and nicotine use by people who have never smoked is rare. More than one-third of current e-cigarette users polled reported smoking cessation and reduction.

Observational studies should also have been considered by the Committee in respect of this question. Jackson et al (2019), for instance, concluded that “use of e-cigarettes and varenicline are associated with higher abstinence rates following a quit attempt”.

Population data can also be used to determine the rate at which e-cigarettes lead to smoking cessation. For instance, Zhu et al (2017) concluded that “The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level”.

Ref:

Nutt (2014). Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach

Mayer (2014). How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century.

OECD (2018). Health at a Glance: Europe 2018. State of Health in the EU Cycle

Radtke (2019). Entwicklung des Raucher- und des Nieraucheranteils unter deutschen Jugendlichen im Zeitraum von 1979 bis 2018

Farselinos (2016). Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries

Jackson (2019). Moderators of real-world effectiveness of smoking cessation aids: a population study.

Zhu (2017). E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys



Scientific_opinion.pdf

597	Farsalinos Konstantinos, University of Patras, Greece	SCIENTIFIC OPINION	<p>Page 17, lines 20-32.</p> <p>The authors argue about the presence of a gateway-to-smoking effects of e-cigarettes using longitudinal studies performed in the US. All these studies included participants who had already tried (or were using e-cigarettes, and compared them with youth who had not tried any product. This behavior of the former group, and the resulting higher odds of using tobacco cigarettes at follow-up, can be easily explained by the common liability model. This model involves mechanisms and biobehavioral characteristics that pertain to the entire course of development of the disorder and changes in the risk [1]. It basically suggests that youth or adults who try e-cigarettes have a general, non-specific tendency to try different things that are not considered conventional or generally acceptable. Therefore, their initial behavior is already a marker of higher tendency to use tobacco cigarettes. By definition, the former group includes risk-prone individuals since they have already initiated a behavior that is considered risky or “rebellious” (e-cigarette use),</p>	See Table 1, answer 5.
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while the latter group are risk-averse individuals.

The common liability model is also the most appropriate model to explain use of different substances that are highly heterogeneous in their clinical phenotype [1]. This has indeed been observed with e-cigarette use, with studies showing that e-cigarette users are more likely to use alcohol and marijuana compared to never e-cigarette users [2,3]. The same model explains their propensity to use tobacco cigarettes. Finally, had e-cigarettes acted as a gateway-to-smoking product, and considering the growing popularity of e-cigarettes among youth in recent years, we would have observed an increase in smoking rates. However, a strong reduction in smoking rates in the US have been observed from 2011 to 2019 (from 4.8% to 2.8% among middle school students and from 15.8% to 5.8% among high school kids) [4]. This largely rejects the gateway-to-smoking hypothesis.

The authors of the Scheer report have failed to consider the most likely scenario, that the common liability model explains the findings which are presented as "gateway-to-smoking" effects.

1. Vanyukov MM, Tarter RE, Kirillova GP, Kirisci L, Reynolds MD, Kreek MJ, Conway KP, Maher BS, Iacono WG, Bierut L, Neale MC, Clark DB, Ridenour TA. Common liability to addiction and "gateway hypothesis": theoretical, empirical and evolutionary perspective. *Drug Alcohol Depend.* 2012 Jun;123 Suppl 1(Suppl 1):S3-17. doi: 10.1016/j.drugalcdep.2011.12.018.

2. Bluestein M, Kelder S, Perry CL, Pérez A. Exploring associations between the use of alcohol and marijuana with e-cigarette use in a U.S.A. nationally representative sample of young adults. *Int J Health Sci (Qassim).* 2019 Jan-Feb;13(1):30-39.

3. Mehra VM, Keethakumar A, Bohr YM, Abdullah P, Tamim H. The association between alcohol, marijuana, illegal drug use and current use of E-cigarette among youth and young adults in Canada: results from Canadian Tobacco, Alcohol and Drugs Survey 2017. *BMC Public Health.* 2019 Sep 2;19(1):1208. doi: 10.1186/s12889-019-7546-y.

4. US Centers for Disease Control. Youth and tobacco use. September 9, 2020. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm

598 Compernelle Thomas, British American Tobacco, Belgium

SCIENTIFIC OPINION

The Scientific Opinion section of the SCHEER Preliminary Opinion which summarizes the risk assessment and general product and product use evaluation for e-cigarettes exemplifies many issues that are common throughout the document and could influence the overall risk assessment outcome. Several main points of commentary are summarized below and expanded on in subsequent comments on the Scientific Opinion (section 3) of the Opinion (P10, LN38).

The potential health benefits of e-cigarette use as a tobacco harm reduction alternative to smoking (1-7) are not meaningfully considered. The assessment should focus on the balance of risks between smoking and vaping and how this affects EU public health considering transitions between smokers, vapers and non-users (P10, LN47: “adverse health effects”; P18, Section 3).

See Table 1, answer 1.

Data derived from studies with either outdated products or only those available outside the EU are included. Risks are discussed in the report based on non-EU and pre-TPD legislation and are therefore not relevant in this context as these e-liquids/products (or resulting derivatives, constituents thereof) are not currently available/applicable in the EU (e.g. P12, LN1-5; P15, LN34; P16, LN21-25).

See Table 1, answer 2.

There is limited/incomplete or inconsistent data (design, methods, measurement) to support risk assessment conclusions. Crucial aspects of SCHEER’s risk assessment, such as choices of Point of Departure studies, exposure measurements and estimates, are not described nor explained in the report. Moreover, in some cases general conclusions about risk (including initiation, cessation) rely on a single, non-peer reviewed study that may or may not include all the information needed to support SCHEER’s overall findings/opinions (e.g. P14, LN20-30).

Unfortunately, these comments are not specific enough to answer correctly. Many of these issues were discussed more elaborately in other comments in this list. See answers to your comments on specific chapters

Confounding factors are not adequately discussed or considered in many of the referenced human behavior studies. Confounding factors such as race, intention to quit, nicotine dependence, etc., can vary across studies and study participants. These factors could have a profound effect on e-cigarette perception, use patterns and cessation outcomes (8).

The Scientific Opinion subsection on initiation (P16) fails to account for the variation in definitions used in many of the referenced studies on initiation of cigarette smoking. Collectively, these limitations invalidate the conclusion that the body of evidence is “strong” for e-cigarette use causing cigarette smoking initiation among youth.

Finally, the Opinion appears to apply different weights of evidence toward overall conclusions reached with respect to various endpoints (e.g. P15, LN5-17). Specifically, with respect to health effects, much of the evidence supporting potential links between e-cigarette use and health outcomes discussed in the Opinion are based on acute and/or in vitro observations. It is made clear in the report that long-term clinical studies are required to make any robust assessment of the health risks presented, as in the case of pulmonary disease. Nevertheless, the SCHEER concludes that similar acute or short-term in vitro observations provide “strong” evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system (P14-15).



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The Opinion has been revised. Please see Table 1 comment 5.

The Opinion has been revised accordingly regarding the health effects of electronic cigarettees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

599	Compernelle Thomas, British American Tobacco, Belgium	SCIENTIFIC OPINION	Data derived from studies with either outdated products or only those available outside the EU are included. Several risks discussed in the report are based on non-EU and pre-TPD publications, that are not relevant to e-liquids currently on the EU market. Concerns of TSNAs as impurities from nicotine in e-liquids are irrelevant as TPD requires ingredients to be of high purity; nicotine being of pharmaceutical grade purity and risks are thus comparable to those from nicotine replacement therapy (P16, LN22). While the Opinion reports that some devices in the US can potentially deliver as much	See Table 1, answer 2.
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nicotine as a cigarette, the evidence is from products containing higher nicotine levels than are allowed in the EU (P12, LN1-5). In contrast to stated evidence that “nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible cigarettes”, other studies show that nicotine uptake from e-cigarettes (up to 4% nicotine) is significantly below that of cigarettes (1-4).

There is limited/incomplete or inconsistent data (design, methods, measurement) to support risk assessment conclusions. Crucial aspects of SCHEER’s risk assessment (choice of Point of Departure studies, exposure measurements and estimates) are not described. Some conclusions are based on a single, non-peer reviewed study that may not enable an objective opinion (P14, LN20-30). For example, conclusions on risks from second-hand aerosol exposure are based on a single study (P14, LN23), using unlikely extrapolations from exhaled breath rather than room air measurements, and assumes exposure scenarios that are unrealistically high compared to the SCHEER assumptions for the risk assessment for the main user. These conclusions could be supported by referral to the 2020 assessment from the UK Committee on Toxicity (5). Another example of limited support underpinning an opinion is the second-hand aerosol exposure assessment, ignoring published studies and relies on a single study that uses an inaccurate method to estimate room air concentrations and assumes highly unrealistic exposure scenarios (P12, LN29-40). While the potential second-hand exposure to non-users of e-cigarettes is likely, the exposure to non-users is several orders of magnitude lower than the exposure to smokers/vapers (more than the single order of magnitude found on P12, LN33). Numerous uncited publications have measured concentrations of secondhand smoke constituents and, with the general exceptions of PG, VG, and nicotine, however are comparable to background concentrations or not detectable (6-8). More examples of incomplete/flawed provision of information were noted with respect to study design, methods or measurements noted within some of the references. Specifically, efforts to assess whether e-cigarette use causes cigarette smoking must consider “common liability” (predisposing factors of e-cigarette use are common to those of cigarette

The SCHEER uses internationally accepted procedures for risk assessment.

smoking). The common liability model, where inclination towards risk-taking and psychosocial processes can be factors, provides a parsimonious explanation of substance use and addiction co-occurrence (P16, LN52 - P17, LN32) (9-11). Some of the systematic reviews in the Opinion do not support the gateway hypothesis (P18, LN35-39), despite SCHEER stating strong evidence. Causal inferences are not supported by the evidence and that youth using both e-cigarettes and cigarettes share a number of risk factors that increase their susceptibility to use either product (9) and are not adequately discussed. In particular, socio-demographic characteristics, willingness to take risks, and perception of comparative cigarette and e-cigarette risks and/or benefits all differentially influence cigarette smoking initiation (12).



C2R0_-EU-Rationale
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600 Compernelle
Thomas, British
American
Tobacco, Belgium

SCIENTIFIC
OPINION

The Scientific Opinion section of this Opinion detailing the risk assessment approach has significant deficits and fails to take into account key factors that could influence the overall risk assessment outcome.

Confounding Factors are not adequately discussed or considered in many of the referenced human use and behavior studies. The Opinion failed to discuss the importance of adjusting for factors between study groups within a given study that could influence the outcomes of interest. For example, different racial or ethnic groups could have different tobacco behaviours and perceptions that may influence cessation outcomes (1). Other confounding factors include intention to quit, which can vary across studies and study participants. These factors could have a profound effect on e-cigarette use patterns and cessation outcomes. Respondents with a higher motivation to quit are more likely to have a successful quit attempt. In a recently completed systematic review and meta-analysis on associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking, 101 studies were identified as investigating the association between e-cigarette use and abstinence from cigarette smoking. Among those studies, the majority (n= 77 studies, 76%) did not adjust for age, race, and sex (2). Thus, pooling a body of evidence with high heterogeneity

See answers to these comments in the specific chapters.

among studies, many of which lack adjustments for confounding factors that influence the observed associations between e-cigarette use and cigarette smoking cessation outcomes, will inherently result in the evidence being graded as “weak.” This issue was also discussed in a systematic review that was included in the Opinion’s assessment of cessation (3).

The Opinion failed to account for the variation in definitions used in many of the referenced studies on initiation of cigarette smoking. The subsection on initiation in the Scientific Opinion section fails to account for the variation in definitions of initiation of cigarette smoking among the studies (P16, Section 2). In most cases, definitions of initiation are more consistent with experimentation (e.g., “ever use”) than true initiation (4-5). Definitions for e-cigarette use and cigarette smoking initiation are inadequate for defining established behaviors. Collectively, these limitations invalidate the conclusion that the body of evidence is “strong” for e-cigarette use causing cigarette smoking initiation among youth. Comparator groups and e-cigarette use definitions are highly heterogeneous across the studies, limiting the overall synthesis of the evidence. For example, the comparator groups in the included randomized trials varied between studies, and included nicotine replacement therapy, nicotine-free e-cigarettes, and support/counselling (3,5-7). In terms of e-cigarette use definitions, the Opinion failed to consider frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation (8).

Ref:

Webb Hooper M, Kolar SK. Racial/ethnic differences in electronic cigarette use and reasons for use among current and former smokers: findings from a community-based sample. *International journal of environmental research and public health*. 2016 Oct;13(10):1009

Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use Among Cigarette Smokers and Changes in Continued Cigarette Smoking. 2020.

Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic cigarettes for smoking cessation: A systematic review. *Nicotine Tob Res*. 2016;18(10):1926-36.

Glasser A, Abudayyeh H, Cantrell J, Niaura R. Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. *Nicotine and Tobacco Research*. 2019;21(10):1320-30.

Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. *N Engl J Med*. 2019;380(7):629-37.

Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead L, Hajek P. Electronic cigarettes for smoking cessation. *Cochrane Database Syst Rev*. 2016;9(9):CD010216.

Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. *Lancet Respir Med*. 2020;8(1):54-64.

Liu X, Lu W, Liao S, Deng Z, Zhang Z, Liu Y, et al. Efficiency and adverse events of electronic cigarettes: A systematic review and meta-analysis (PRISMA-compliant article). *Medicine (Baltimore)*. 2018;97(19):e0324.

601 Compernelle Thomas, British American Tobacco, Belgium

SCIENTIFIC OPINION

The Scientific Opinion section of this Opinion detailing the risk assessment approach has significant deficits and fails to take into account key factors that could influence the overall risk assessment outcome.

Incongruent Weight of Evidence Application: The Opinion appears to apply different weights of evidence toward overall conclusions reached with respect to various endpoints. Specifically, with respect to health effects, much of the evidence supporting potential links between e-cigarette use and health outcomes discussed in the Opinion are based on acute in vitro observations. Although it is made clear in the report that long-term studies are required to make any robust assessment of the health risks presented, the Opinion nevertheless concludes that similar acute or short-term in vitro observations provide strong evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system.

SCHEER treats cessation as a monolith, when in fact measures of cessation varied considerably and were often unique outcomes that should not be collectively grouped, e.g., 7-day point prevalence abstinence is a far different outcome than 12-month abstinence. The outcome measures should have been described and appropriately considered as unique measures (1). Failure to do so compromises the validity of the weight of evidence cited in the Opinion.

Additionally, the recent systematic review, which used a rigorous methodology to assess the weight of evidence for individual cessation measures, found that at present, there is insufficient

See answers to these comments in the specific chapters.

evidence to support a conclusion that e-cigarette use is positively associated with continued cigarette smoking (2). The Opinion may have applied different weights of evidence for individual cessation measures, as observed in the recent systematic review (2). However, when combining cessation measures as a monolith, the weight of evidence should not have been “low” but rather “not possible.” The Opinion failed to consider frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation. The Opinion lacked the adequate justification for its evaluation of the strength of evidence as “weak” for cessation and “weak to moderate” for reduction. Given the variations in key parameters across the studies examining cigarette smoking cessation, heterogeneity was inevitable—and the studies should not have been synthesized as a single body of evidence.

Ref:

1. Glasser A, Abudayyeh H, Cantrell J, Niaura R. Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. *Nicotine and Tobacco Research*. 2019;21(10):1320-30.

2. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic cigarettes for smoking cessation: A systematic review. *Nicotine Tob Res*. 2016;18(10):1926-36.

602	Schulz Thomas,G erman Federal Institute for Risk Assessment,Germany	SCIENTIFIC OPINION	<p>General remarks</p> <p>The report has a high quality and covers many aspects of E-cigarette use citing latest re-search papers in the field. It gives a comprehensive overview and assessment of important issues regarding electronic cigarettes and highlights knowledge gaps.</p> <p>However, there are some points for improvement especially regarding the link to hazard statement codes of the CLP regulation, which should be either removed or revised.</p>	Thank you. The points of improvement have been addressed.
603	Lund Karl Erik,Norwegian Institute of Public Health,Norway	SCIENTIFIC OPINION	<p>Page 16 Line 30–50: - when discussing the increase in vaping among young people in the US, please note that the trend for smoking and the trend for vaping among young are inversely correlated. Trends for the two behaviors should not be studied separately.</p> <p>P 17 L 1-13: - when reviewing the literature on perception of e-cigarettes among youth, please be aware the finding from a qualitative longitudinal study following young adolescents in Norway from ages 12 to 17 (Tokle R 2020) concluding: “.....vaping</p>	<p>See Table 1, answers 6 and 7.</p> <p>Please see Table 1 comment 5.</p>

had lost status and was described as ‘childish’ and unpopular.. comparing e-cigarettes with the fidget-spinner and reserving vaping for kids and addicted adult smokers. E-cigarettes were devalued from novelty and transgression to childish and uninteresting within the same sample over a four-year period. In conclusion, e-cigarettes in the sample represented fashionable experimentation rather than steady user patterns”

P 17 L 20-32: - the opinion on the role of electronic cigarettes as a gateway to smoking is based on results from longitudinal studies where a cohort of non-vaping youths serve as a basis for comparison with another cohort of vaping youth (e.g Soneji et al 2017, Chatterjee, et al., 2016, Glasser, et al.,2019 etc). When interpreting these studies, please note that these two groups may have important differences. Precisely because the latter group are users of e-cigarettes, they demonstrate a willingness to perform a norm-breaking behavior at baseline. Thus, these studies compares the risk of starting to smoke in two groups, which are different when it comes to the tendency to commit a risky act - and thus also probably differ in other characteristics. These studies compares the probability of starting to smoke in a group with risk aversion, with a group who already use a nicotine product defined at baseline as socially undesirable and risky. The possibility that unadjusted confounders could cause the statistical association with subsequent smoking observed in longitudinal studies can not be ruled out.

Please see Table 1 comment 5.

P 18 L 1-6 - when stating opinion regarding the possible problems caused by the appeal from flavoured e-liquid, it is helpful to apply a risk/use equilibrium where potential advantages are weighted against potential disadvantages. Given the level of exposure to toxicants for never-smokers who take up vaping, and given the (toxicologically verified) large reduction in exposure to toxicants for smokers who switch to e-cigarettes, the number of never-smokers taking up e-cigarettes prompted by flavours must be implausibly large to balance out the assumed health gain from the smokers who make a flavour-driven product switch to e-cigarettes

See Table 1, general answer 1.

Ref: Tokle, R. (2020). ‘Vaping and fidget-spinners’: A qualitative, longitudinal study of e-cigarettes in adolescence. *International Journal of Drug Policy*, 82, 102791.

604 Machalska Magdalena, European Society of Cardiology, Belgium SCIENTIFIC OPINION

ESC welcomes the SCHEER preliminary opinion on e-cigarettes and the evidence it provides on the risks of systemic effects of e-cigarettes on the cardiovascular system. This response is submitted on behalf of the ESC, and the European Association of Preventive Cardiology (EAPC), part of the ESC & is based on EAPC position paper on e-cigarettes and health with special focus on CV effects (pdf attached). As stated by the SCHEER Opinion, LT effects of the use of e-cigarettes on the CV system are still unknown due to the lack of relevant data. More longitudinal research studies, investigating multiple subclinical and clinical effects of e-cigarettes smoking on the CV system, are needed. While LT cardiovascular effects of the use of e-cigarettes remain largely unknown, the existing evidence & data gathered by the EAPC & based mainly on non-randomised observational studies, suggests that e-cigarettes should not be regarded as a safe product as they may lead to potential CV harm through mechanisms that increase the risk of thrombosis and atherosclerosis amongst others. Harmful CV effects have also been assessed indirectly based on documented toxicity of various constituents as well as on mechanistic studies. The meta-analysis demonstrated that the exposure to e-cigarettes increases heart rate, systolic blood pressure, and diastolic blood pressure. Even small increases in blood pressure in the population have significant effects on CV health. Harmful LT impact on vascular wall growth was illustrated. Furthermore, emerging evidence suggest that nicotine, irrespective of its source (i.e. e-cigarettes, tobacco), directly contributes to acute CV events in the presence of ischaemic heart disease & could impair vascular function & lead to vascular calcification. It should be noted, however, that the amount of nicotine delivered by e-cigarettes, may vary depending on several factors: nicotine concentration in the e-cigarette's liquid, user experience, puffing intensity & device characteristics. Moreover, the potential decrease of harm induced by e-cigarettes (vs conventional tobacco), as suggested in the SCHEER Preliminary Opinion, may in part be offset by its increased use, in particular by vulnerable groups such as adolescents & young people. Even though selling e-cigarettes to anyone under 18 years old is illegal in many countries, the legislation is not harmonised & often ignored. Although framed by the EU Directive on Tobacco products, legislation on e-cigarettes is new & there is no consensus on how to legislate the sales, packaging, taxing, and public use. The rapid evolution of the e-cigarettes market has outpaced the legislator's regulatory capacity, leading to mixed regulations & possibly illegal actions. Selling products like e-cigarettes to the youngest comes with many risks, including that never-smokers minors who use e-cigarettes might double their chance of starting to smoke cigarettes in a later stage of their life, as demonstrated by the research included in the position paper published by the EAPC. Thus,

Thank you for your support. The SCHEER took into account your important consideration ... "Until such research is available, e-cigarettes should only be considered to support smoking cessation for a limited time & under medical supervision. E-cigarettes are not recommended as a LT alternative to smoking cessation, because there is a lack of robust evidence that these are effective" in the revised Opinion.

harmonization&implementation of existing regulation are necessary as well as setting of swift procedures to adopt regulation&taxation to incoming evidence. The role of governments and NGOs is essential to encourage and support ethically&appropriately designed research investigating e-cigarettes smoking effects on the CV system. Until such research is available, e-cigarettes should only be considered to support smoking cessation for a limited time&under medical supervision. E-cigarettes are not recommended as a LT alternative to smoking cessation, because there is a lack of robust evidence that these are effective. E-cigarettes should not be used for this purpose instead of evidence-based smoking cessation methods&products.

Ref:

Kavousi (2020). Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). DOI: 10.1177/2047487320941993

605	Vuerich Michela, ANEC, European Consumer voice in standardisation, Belgium	SCIENTIFIC OPINION	<p>Page 11, lines 8-14: SCHEER focuses on nicotine, carriers and ingredients depending on their frequencies and amounts measured. This approach should be complemented by identifying substances which have been already subject to assessments and found potentially unsafe irrespective of frequencies and amounts measured. Otherwise substances which are found less frequently and/or at lower concentrations may be overlooked.</p> <p>Page 11, lines 38-41: In order to determine exposure "specific information on consumer behaviour was collected regarding the frequency of use, number of puffs, puff duration, puff volume and puff interval". These parameters vary strongly as SCHEER rightly states. Hence, a reasonable worst case exposure must be defined.</p> <p>Page 12, lines 49-51: It is difficult to understand that the lack harmonised classification does not allow a risk assessment and why classifications notified by industry are not considered relevant by SCHEER. For some substances extensive reviews identifying hazards and risks related to inhalation used in e-liquids or found in emissions are available from other areas. For diacetyl, such reviews are e.g. available from SCOEL and NIOSH. Such reviews should be identified by SCHEER.</p> <p>Page 13, lines 23-24: SCHEER rightly underlines the importance of child resistant features to prevent accidental poisonings.</p>	<p>Risk comparison is outside the scope of this assessment.</p> <p>The risk assessment was based on use topography of a light, average and heavy user.</p> <p>The SCHEER used all hazard classification as considered appropriate.</p> <p>Thank you for your opinion. For SCHEER, this is outside the mandate.</p>
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However, the TPD does not specify the requirements for child resistance – neither for the e-cigarettes nor the e-liquids. This is a serious omission.

Page 13, lines 33-34: The limited number of notifications of faulty products to the Rapid Alert System may among other be the result of lacking child resistance specifications and indicate a lack of resources of market surveillance authorities. A lack of notifications is not necessarily an indicator of good safety.

Page 14, lines 4-18: It is undoubtedly true that intermittent exposure patterns with very high peak values followed by interruptions pose a challenge. It is also true that direct (!) comparisons between exposures from e-cigarettes and health based guidance values (HBGVs) are normally inadequate but such limits and the underlying toxicity data may nevertheless be a departure point for assessing risks or deriving acceptable thresholds by calculation or modification. We wonder why systemic long-term effects could not be assessed using the daily dose metric given that SCHEER itself refers to studies which calculated a MoE based on a daily dose (e.g. Visser for systemic effects).

Page 15, lines 36-38: Whilst SCHEER declares on page 14 that comparisons between HPGV values and measured exposures are inadequate SCHEER concludes on page 15 that "the weight of evidence for adverse effects from the metals in aerosols, specifically carcinogenicity, is weak" and that "this conclusion is mainly based on the comparison between measured exposure levels in aerosols and health-based guidance values". So what?

Page 15, lines 45-47: SCHEER claims that "there is no specific data that specific flavourings used in the EU pose health risks for electronic cigarette users ". Apparently SCHEER ignored that several flavouring compounds have already been subject of discussion and normative restrictions.

Page 18, lines 35-36: SCHEER holds the opinion "that there is strong evidence that electronic cigarettes are a gateway to smoking

The Opinion has been adapted.

The SCHEER adopted the method of Visser et al based on inhalatory data, estimation of the maximum alveolar concentration for local effects and the total absorbed daily dose for systemic effects to arrive at the MoE (see Section 6.5.5.3) .

The SCHEER argues in the risk assessment section that risk assessment comparing exposure with HBGVs are not applicable for the purpose of this Opinion, unless they show that the puff concentrations measured are below these standards and therefore clearly point at the absence of any risk with a wide margin. This is largely the case for metals in the studies cited (section 6.5.5.4).

This comment is not clear.

See Table 1, answer 5.

			for young people" without discussing the literature opposing the gateway theory.	
606	Vuerich Michela, ANEC, European Consumer voice in standardisation, Belgium	SCIENTIFIC OPINION	<p>Page 11, lines 8-14: SCHEER focuses on nicotine, carriers and ingredients depending on their frequencies and amounts measured. This approach should be complemented by identifying substances which have been already subject to assessments and found potentially unsafe irrespective of frequencies and amounts measured. Otherwise substances which are found less frequently and/or at lower concentrations may be overlooked.</p> <p>Page 11, lines 38-41: In order to determine exposure "specific information on consumer behaviour was collected regarding the frequency of use, number of puffs, puff duration, puff volume and puff interval". These parameters vary strongly as SCHEER rightly states. Hence, a reasonable worst case exposure must be defined.</p> <p>Page 12, lines 49-51: It is difficult to understand that the lack harmonised classification does not allow a risk assessment and why classifications notified by industry are not considered relevant by SCHEER. For some substances extensive reviews identifying hazards and risks related to inhalation used in e-liquids or found in emissions are available from other areas. For diacetyl, such reviews are e.g. available from SCOEL and NIOSH. Such reviews should be identified by SCHEER.</p> <p>Page 13, lines 23-24: SCHEER rightly underlines the importance of child resistant features to prevent accidental poisonings. However, the TPD does not specify the requirements for child resistance – neither for the e-cigarettes nor the e-liquids. This is a serious omission.</p> <p>Page 13, lines 33-34: The limited number of notifications of faulty products to the Rapid Alert System may among other be the result of lacking child resistance specifications and indicate a lack of resources of market surveillance authorities. A lack of notifications is not necessarily an indicator of good safety.</p> <p>Page 14, lines 4-18: It is undoubtedly true that intermittent exposure patterns with very high peak values followed by</p>	See answers to comment 605.

interruptions pose a challenge. It is also true that direct (!) comparisons between exposures from e-cigarettes and health based guidance values (HBGVs) are normally inadequate but such limits and the underlying toxicity data may nevertheless be a departure point for assessing risks or deriving acceptable thresholds by calculation or modification. We wonder why systemic long-term effects could not be assessed using the daily dose metric given that SCHEER itself refers to studies which calculated a MoE based on a daily dose (e.g. Visser for systemic effects).

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Page 18, lines 35-36: SCHEER holds the opinion "that there is strong evidence that electronic cigarettes are a gateway to smoking for young people" without discussing the literature opposing the gateway theory.

607 Clark Alex, The Consumer Advocates for Smoke-free Alternatives Association (CASAA), SCIENTIFIC OPINION

Pg. 18 - Lines 4 and 23
 Throughout the SCHEER report, a "popular pod device with a 76% US-market share" is referenced. The SCHEER statement lacks context. The penultimate source referenced by Fadus, et al contextualizes this number by noting that JUUL's market share is only measured as a percentage of Neilson-tracked retail channels. There remains a large segment of the vapor industry that is not tracked by Neilson and is estimated to make up 30% to >50% of the overall nicotine vapor market. "E-cig category dollar sales were \$408.5MM this period implying about ~\$4.6B annual retail sales in Nielsen-tracked channels (vs \$3.3B in 2018). Considering Nielsen

This has been replaced throughout the report by a 'large market share'.

Thank you for the comment:
 The text of the Opinion was amended.

See also the answer to question 15.

	United States		underestimates and doesn't capture all of the channels where e-cigs/vapor products are sold such as online, vape shops, etc, we estimate the total category will reach approximately \$9.0B by the end of 2019 (vs ~\$7.0B in 2018)." Ref: Herzog, Bonnie, and Patty Kanada. Wells Fargo, 2019, pp. 11, Nielsen: Tobacco All Channel Data Thru 9/7 - Cig Vol Declines Hold Steady.	
608	Woessner Julie, International Network of Consumer Organizations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	SCIENTIFIC OPINION	The Scientific Opinion summarizes many of the issues explored in more depth in the body of the Preliminary Opinion. We have provided substantive comments on those sections, but note here that this section is one of the three sections (Abstract, Summary, Scientific Opinion) that many, if not most, people will rely upon to gain an understanding of SCHEER's findings. Therefore, the selection of the information to be contained in this section is crucial to avoid misleading or misinforming readers. Page 10 / Line 54 Replace "nicotine" with "high-purity nicotine". The TPD allows only this kind of nicotine in vaping liquids, Art 3(d). The same replacement should be done throughout the entire opinion regarding EU products. See our comment in TERMINOLOGY. Page 11 / Lines 2-4 Many countries are producing vaping products, including European countries, and we are unclear as to why SCHEER places so much emphasis on the US? Page 11 / Lines 50-51 We ask the SCHEER to add that the exposure level is orders of magnitude lower for bystanders. We note that for many people, the Scientific Opinion section will be the portion of SCHEER Opinion that they will rely on to gain an understanding of SCHEER's position. This information is important for readers to have relevant context. Page 12 / Line 2 SCHEER should replace "smoking habits" with "nicotine use patterns" in order to take into consideration all cases, including users who stopped smoking.	Thank you for your comment. See Table 1, answer 4. See Table 1, answer 8. This conclusion was already in the preliminary Opinion: see conclusions of risk assessment for second-hand exposure. The SCHEER agrees. Opinion is amended.

			Page 12 / Line 3-5	SCHEER should clearly state that there is a big difference between tobacco cigarettes and e-cigarettes in that the nicotine from vaping in the EU is high-purity nicotine, without tobacco additives and without combustion.	See Table 1, answers 1 and 4.
			Page 12 / Lines 12-13	Using “smoking protocols” is misleading. It should be replaced with “electronic cigarette use protocols” as defined in SCHEER’s own terminology, page 19.	This has been corrected throughout the Opinion.
			Page 12 / Lines 19-27	SCHEER uses the term “particles” while using the term “droplets” in other sections of their preliminary Opinion. We ask SCHEER to clearly state the difference between the two terms and include a comparison with tobacco smoke particles.	This is described later in the Opinion (section 6.5.2.1 Aerosol characteristics).
			Page 13 / Lines 19-24	SCHEER should recall here that the current TPD greatly limits these risks.	Thank you for your comment.
			Page 13 / Lines 40-43	Long-term use of high-purity nicotine in NRTs does not show substantial risks. Therefore it can’t simply be assumed that mechanisms similar to tobacco smoke exist when talking about exposure to high-purity nicotine from electronic cigarette use.	Please see sections 6.5.4 and 6.5.5.
			Page 13 / Lines 46	To provide a clear understanding of the differential risks, SCHEER should replace “electronic cigarette use has harmful health effects” with “electronic cigarette use isn’t harmless but is much less harmful for health than smoking”.	The Opinion does not need a revision in this paragraph.
			Page 14 / Line 39-41	SCHEER assesses the weight of evidence but doesn’t qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is moderate.	See Table 1, answer 1. The SCHEER does not agree. It is clear from the wording that moderate pertains to the WoE.
609	Woessner Jullie,Inter	SCIENTIFIC OPINION	Page 15 / Lines 1-3	The bold emphasis is misleading because it gives the impression	The SCHEER does not agree. It is clear from the wording that moderate pertains to the WoE.

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the EU

that the risk itself is strong when it's just the weight of evidence that SCHEER has judged strong. The emphasis should be on "the risk is expected to be low".

Page 15 / Lines 5

Typographical error: "rosk" should be replaced with "risk"

Thank you, it has been corrected.

Page 15 / Lines 5-6

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is strong.

A fully quantitative risk assessment was not possible. Therefore SCHEER based the risk assessment on a weight-of-Evidence assessment including different lines of evidence. One of the lines of evidence for various endpoints is based on the estimation of the MoE, a semi-qualitative risk value.

Page 15 / Lines 19-22

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak to moderate.

Page 15 / Lines 36-38

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself.

Page 15 / Lines 40-43

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself.

Page 16 / Lines 2-3

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is moderate. In this case it's especially misleading because the third line of evidence states: "Exposure of second-hand exposed persons to glycerol or aldehydes is negligible or orders of magnitude lower than for electronic cigarette users."

Page 16 / Lines 12-14

SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading

because it gives the impression that the risk itself is weak to moderate.

Page 16 / Lines 21-22
SCHEER assesses the weight of evidence but doesn't qualify/quantify the risk itself. The bold emphasis is misleading because it gives the impression that the risk itself is weak to moderate.

Page 18 / Lines 35-39
We question how SCHEER ends up with such a strong opinion on a gateway hypothesis when the evidence is so weak in the EU and in the US? See our comment in TERMINOLOGY on the gateway hypothesis.

See Table 1, answer 5.

Page 19 / Lines 1-7
We question how SCHEER and the 2020 Cochrane Review, within basically the same timeframe with basically the same data at their disposal, end up with such different opinions. See our comments in 6.7 Role of electronic cigarettes in the cessation of traditional tobacco smoking and dual use.

See Table 1, answer 6.

610 Woessner SCIENTIFIC
Julie, Intern OPINION
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Page 11, Lines 2-4

SCHEER states "There are currently four generations of electronic cigarettes in the EU market, but this evolves in a very rapid way and other products, already marketed in the USA, are expected to come soon".

INNCO refutes the assertion that products already marketed in the USA, are expected to come [into the EU] soon. The comment seems to suggest that the EU is being bombarded by new generations of e-cigarette products which 'might pose unknown threats to health'.

In reality, whilst products are constantly being refined (usually to incorporate even more reliable functions and materials), the arrival of entirely new generations of products are markedly few.

The majority of models on general sale are well known branded

The text is amended to include the fifth generation. The new edition does not comment on the US market's influence.

15 from
the EU

products and whilst a miniscule number of niche products may be available via limited specialist retailers, the majority of e-cigarettes products remains broadly ubiquitous throughout Europe and the USA. Moreover, we note that offerings coming from the USA will likely be more limited in coming years due to the enforcement of the Premarket Tobacco Product Application (PMTA) requirement associated with the Family Smoking Prevention and Tobacco Control Act, which will dramatically limit the availability of new products in the USA. The major difference between the markets in the US and the EU is based upon legislation and restrictions placed on the market.

This is a correct statement and does not affect the opinion's conclusion.

It is important to note that the TPD provides limitations that naturally restrict many of the newer products from the USA, here referring to the 2ml tank limitations and the 20mg/ml imposed by the TPD.

It has been already in the opinion. Thank you.

611 Brose
Leonie
,King's
College
London,Un
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Kingdom

SCIENTIFIC
OPINION

Page 16, lines 27-50. Role of electronic cigarettes as a gateway to smoking/the initiation of smoking, particularly for young people. I am not commenting on the discussion of 'gateway' that is provided. Instead, I am merely commenting on the prevalence figures presented as an example highlighting some of the substantial weaknesses of the evidence synthesis.

Please see Table 1, answers 5, 6, 12.

Page 16, lines 30-31: "Electronic cigarettes are rapidly becoming a new trend among adolescents and the number of users increased from 7.2% in 2012, to 11.6% in 2014 to 14.6% in 2017 in the EU." This statement is incorrect. The prevalence figures are presented without a source. Searching for them in other places indicate that these are from the Eurobarometer (referenced as Laverty et al, 2018 in the opinion). However, they are not the number of users among adolescents but the proportion of those aged 15 and over in the European Union who have ever tried an e-cigarette. Ever trial is not synonymous with use and while all aged 15 and over include some adolescent but are not representing adolescents as stated.

Page 16, lines 32-35: "...15% of the respondents have at least tried electronic cigarettes and 2% use them regularly. Among young people (15-24 years), ever use is higher than average (25%), a substantially higher rate than experimentation in other age

categories” It would be far more informative and relevant to public health outcomes and the heading of this section to report regular use among young people and not restrict this statement to experimentation when data on regular use are clearly available.

Page 16, lines 42-45: “A more recent review on the prevalence of electronic cigarette use among the general adult and young populations in Europe concluded that the prevalence of current electronic cigarette use ranged from 0.2% to 27%, ever-use ranged from 5.5% to 56.6% and daily use ranged from 1% to 2.9%.” These present a range but give no indication of the source of the data, the quality of the study, the representativeness of the data or the distribution of the prevalence figures across studies, thereby indicating that the full range of figures were equally common and representative of the population. To give some examples, the 27% prevalence of current electronic cigarette use referred to a survey of a sample of students in one disadvantaged rural district in Poland and data were not weighted to be representative. Similarly, the 56.6% ever use come from a survey of students in Lithuania attending selected faculties who were aged 18-34. To be informative, figures should be weighted (eg taking into account size of the sample, quality of the data collection) and an overall summary provided. It should also be clarified which populations each figure refers to and figures for young reported to be relevant to the heading of this subsection.

Page 16, lines 47-49: “having ever used electronic cigarettes was 5.75 times more likely among 18-24 year olds compared to those >55 years of age” Without the actual prevalence figures for ever use in these groups, this provides no information about young people

Page 16, lines 49-50 “however, adolescents were less likely to be regular user than those aged ≥ 55 years 50 (16.9% vs. 38.1%)”. This is a misinterpretation of the data. It is not the proportion of regular users in these age groups but the proportion of ever regular users out of those who had ever tried. For example: 25.0% of those aged 15-24 (here described as ‘adolescents’) had ever tried e-cigarettes

612 Grigg Jonathan, European Respiratory Society, Belgium

SCIENTIFIC OPINION

and 16.9% of those are described as having become regular (at least weekly) users at any point in time.

Our comments concern the section: Scientific Opinion Overall assessment for electronic cigarette users P14 L32 through to P15 L52.

We concur with the general finding that there is a lack of long-term data. We agree with the conclusion on CNS. However, we find that the conclusion on pulmonary disease is somewhat confusing and weak. To our best knowledge, there exists as much long-term data on pulmonary disease as on cardiovascular disease, and in both cases the evidence shows that there probably is an increased risk of disease by long-term exposure. In vivo experiments as well as animal studies have demonstrated airway inflammation and remodeling/scarring 1 2 3 4 5 and impairments in lung function 6 7. Exposure to e-cigarette fluid promoted respiratory viral infection 8 and bacteria became more virulent when exposed to ecigarette vapour 4. Human experiments have shown airway obstruction⁹, induced transient lung inflammation and gas exchange disturbances 10 and dysregulation in normal human lung homeostasis after short-term inhalation 11. A study studying sputum of e-cigarette users found altered profile of innate defense proteins in airway secretions, inducing similar and unique changes relative to cigarette smoking 12. Another human study found that chronic vaping disrupts the protease-antiprotease balance by increasing proteolysis in lung, which may place vapers at risk of developing chronic lung disease 13. Animals exposed to e-cigarette vapor showed a disorganization of alveolar and bronchial epithelium 14 and higher mortality when exposed to virus infection and neonatal exposure showed impairment in postnatal lung growth. Animals exposed to chronic vaping developed asthma, COPD⁷ and lung cancer 15. In addition, there is moderate evidence from population based studies for increased respiratory symptoms in adolescents and adults and an increase in asthma exacerbations 16 17 18 19 20 21 . Even in adolescent never-cigarette users, risk of bronchitic symptoms has been found to be significantly elevated, after adjustment for relevant potential confounders 22. Longitudinal studies have shown increased risk of COPD exacerbations 23 and incident respiratory disease 18.

Already in 2017 a review concluded 24: “There is a rapidly growing body of evidence derived from in vitro, animal, and human studies that e-cigarette use may have significant pulmonary toxicity”.

A recent review concluded 25: “Inhalation of e-cigarette aerosols impacts pulmonary physiology, with short-term exposure leading to increased airway reactivity, while long-term exposure leads to increased airway

The SCHEER thanks for the critical review.

Concerning the conclusion on pulmonary diseases different lines have been reported:

- 1) risk for carcinogenicity of the respiratory tract → weak to moderate
- 2) adverse effects from the metals → weak
- 3) long-term adverse health effects, such as pulmonary disease → lack of consistent data
- 4) inhalation toxicological data of specific flavourings
- 5) inhalation toxicological data of flavourings → weak

Admittedly, these five different assessment make it somewhat confusing, but all assessment are analysed in separate sections in the Opinion and summarised in this section

In the final version, the fourth and fifth point have been separated in two distinct paragraphs for clarity

resistance, airway obstruction and inflammation. Both short-term (weeks to months) and long-term (years to decades) inhalation of e-cigarette aerosols increase lung inflammation and airway reactivity, raising the concern that vapers will develop asthma, chronic obstructive lung disease (COPD) and chronic bronchitis”. Another recent review (on pulmonary health) concluded 26: “Studies show measurable adverse biologic effects on organ and cellular health in humans, in animals, and in vitro”. “We conclude that current knowledge of these effects is insufficient to determine whether the respiratory health effects of e-cigarette are less than those of combustible tobacco products”.

A newly published study found that among never tobacco users, the adjusted odds of reporting lung disease (diagnosed with COPD, emphysema, or chronic bronchitis) were more than 4 times higher among everyday e-cigarette users than among never e-cigarette users 27. The study had adjusted for 15 sociodemographic and health behavior factors.

SHEER recognizes that e-cigarettes are toxic to the pulmonary system. However, it is difficult for those who are not health professionals to understand the meaning of “toxicity” and the consequences of this, when it comes to diseases such as COPD and asthma.

In light of the above we strongly suggest that the conclusions on the pulmonary system are drafted in a similar way as those concerning the cardiovascular system, stating there is an increased risk of disease by long-term exposure.



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613 Solimini Renata, Istituto Superiore di Sanità, Italy
SCIENTIFIC OPINION

Chapter 3.1 - Page 13, lines 11-13: although it is written that you consider only non-counterfeit products, and that this Opinion covers electronic cigarette products complying with the TPD (Introduction at page 20, lines 26-31), it is not clear (at least to me) if your conclusions about health effects (acute and long-term) and use, especially among adolescents and young people, are all based on literature considering only products compliant to TPD? I think it is difficult to ascertain it.

The SCHEER based the Opinion on the information available, being aware that some of the products studies may not be compliant with TPD. The SCHEER focusses this Opinion on the most frequent chemicals originally used in e-liquids and others that may be generated by chemical reactions through heating of the e-liquid and/or the device itself and to which users of electronic cigarettes may be exposed to through the inhaled aerosol.

Consumers can modify or add substances (chemicals, compounds,

ingredients or combination of ingredients such as a broad range of chemicals, including nicotine, tetrahydrocannabinol (THC) and other cannabinoids, along with cutting agents/diluents and other additives, pesticides, opioids, poisons, heavy metals, and toxins) to vaping products other than those intended by the manufacturers and this may affect the health impacts, including effects on second-hand exposed subjects (they cannot know which substance you are vaping), frequency, and patterns of consumer use of the products. Often materials are added and modifications are made to vaping products (self-made e-cig and liquids) by the users after the manufacturing process. Users can have access to large volumes of nicotine containing liquid.

The scientific literature on electronic cigarettes (e-cig), since 2010-2011, reports the use of this device to inhale substances other than nicotine and/or aromas.

According to the 2011 Etter and Bullen survey, out of a sample of 3,587 e-cigarette users, 0.9% (n = 27) said they had inhaled substances other than the intended liquid such as cannabis, herbs, vodka, and vitamins (Etter and Bullen, 2011).

The National Institute on Drug Abuse (NIDA) underlines how electronic cigarette cartridges can also be refilled with other substances, other than nicotine or aromas, thus becoming a new and potentially dangerous tool for inhaling other pharmacologically active substances (NIDA 2015). This risk is also already reported by WHO in the Electronic nicotine delivery systems report, in which it is noted that some e-cig users modify the product themselves to inhale other substances.

The 2015 literature review by Giraud et al. reports that cannabis smokers have found a new method of inhaling the substance in e-cig. Users of e-cig for inhaling cannabis believe that its use is less detectable as the typical smell of cannabis is masked by the use of different flavors.

The recreational use of e-cig also involves cannabinoids such as cannabidiol, cannabigerol, and other illicit substances such as

methamphetamines, cocaine, heroin, cathinones and powerful hallucinogens such as dimethyltryptamine. Forums and websites talk about the use of e-cigs to inhale numerous substances. In the literature review by Castellanos and Gralnik, published in 2016, it is highlighted how synthetic cannabinoids are also consumed by adolescents through the electronic cigarette (Castellanos and Gralnik, 2016). The 2016 study by Morean et al. reports growing evidence that young e-cigarette users are also multi-drug users. Young people classified as marijuana and alcohol users may start using e-cigs to inhale vaporized cannabis and subsequently switch to more regular use of electronic cigarettes.

Ref:

Castellanos D, Gralnik LM. Synthetic cannabinoids 2015: An update for pediatricians in clinical practice. *World J Clin Pediatr.* 2016 Feb 8;5(1):16-24.

Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011;106(11): 2017–28.

Giroud C, de Cesare M, Berthet A, Varlet V, Concha-Lozano N, Favrat B. E-Cigarettes: A Review of New Trends in Cannabis Use. *Int J Environ Res Public Health.* 2015 Aug 21;12(8):9988-10008.

Morean ME, Kong G, Camenga DR, Cavallo DA, Simon P, Krishnan-Sarin S. Latent class analysis of current e-cigarette and other substance use in high school students. *Drug Alcohol Depend.* 2016 Apr 1;161:292-7.

NIDA. DrugFacts: Electronic Cigarettes (e-Cigarettes). Bethesda: NIDA; 2015. <https://www.drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes>

WHO. Electronic nicotine delivery systems. Conference of the Parties to the WHO Framework Convention on Tobacco Control. Moscow: WHO; 2014. http://apps.who.int/gb/fctc/PDF/cop6/FCTC_COP6_10Rev1-en.pdf?ua=1

614 No agreement to disclose personal data
SCIENTIFIC OPINION

P.10, 147: As an introductory statement, ANAFE would like to underline some methodological inconsistencies in the elaboration of the preliminary opinion. In particular, it is key to point out how the SCHEER takes into consideration some elements from scientific studies comparing the consequences of electronic cigarettes' use with that of traditional tobacco, failing to keep the same approach throughout the opinion. For instance, in next sections the preliminary opinion reports that the nicotine-intake level of electronic cigarettes can be comparable to that of traditional cigarettes; on the contrary, there are no accurate comparisons regarding the difference in cardiovascular and carcinogenic risk deriving from the use of electronic cigarettes compared to that deriving from traditional tobacco.

Please see Table 1, answer 1.

p.11, 16: These are not the only differences between EU and US markets. ANAFE believes it is not possible to infer conclusions with regard to the EU market on the basis of US market features and developments, given the profound and structural differences mainly related to the existing regulatory framework, but also to cultural and social aspects.

Please see Table 1, answers 4 and 8.

p.12, 15: Although electronic cigarettes, nicotine replacement therapies (NRT) and traditional cigarettes offer similar levels of nicotine intake, the former two emit substantially fewer carcinogenic components. As Shahab et al (2017) shows, no clear between-group differences in salivary or urinary biomarkers of nicotine intake were found. However, the e-cigarette-only and NRT-only users had significantly lower metabolite levels for TSNAs (including the carcinogenic metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol [NNAL]) and VOCs (including metabolites of the toxins acrolein; acrylamide; acrylonitrile; 1,3-butadiene; and ethylene oxide) than combustible cigarette-only, dual combustible cigarette-e-cigarette, or dual combustible cigarette-NRT users. The e-cigarette-only users had significantly lower NNAL levels than all other groups. Combustible cigarette-only, dual combustible cigarette-NRT, and dual combustible cigarette-e-cigarette users had largely similar levels of TSNA and VOC metabolites (doc. 1). Also, Shiffman et al (2020) assessed dependence among current and former adult e-cigarette users on cigarettes and e-cigarettes, compared with dependence on cigarettes. Results show how addiction to liquid nicotine and e-cigarettes in general is much less strong and has less impact than traditional cigarettes (doc. 2).

615 No agreement to disclose personal data
SCIENTIFIC OPINION

p.13, 124: During the whole opinion, the SCHEER fails to recognize that most of the risks discussed are already addressed by existing effective EU law provisions through the Tobacco Products Directive (e.g. child-proof fastening and opening mechanism, anti-counterfeit measures etc.).

Risk management is outside the mandate of SCHEER

p.15, 117: There are several studies that do not reflect the position expressed in the SCHEER opinion. For instance, according to Ikonomidis et al (2020), electronic Cigarette vaping for four

The Opinion has been revised accordingly regarding the health effects of electronic cigarettees and particularly on CVD. In particular, the level of evidence is now “moderate” and additional clarifications have been made.

months, has a neutral effect on platelet aggregation of healthy smokers. Results from the analysis on forty smokers of the effects of electronic cigarette on platelet and vascular function after 4 months of use compared to tobacco smoking show that continuation of tobacco cigarette smoking further deteriorates platelet function during 4 months of use. On the contrary, electronic cigarette vaping improves arterial elastic properties and oxidative stress after 4 months of use (doc. 3).

See Table 1, Answer 1.

It is pivotal to highlight here that electronic cigarettes' use should be compared to traditional tobacco cigarettes when analysing health effects, since SCHEER performs this exercise as far as nicotine intake levels are concerned.

In doing so, we noted that, as highlighted by George et al (2019), within 1 month of switching from tobacco cigarettes to e-cigs, smokers demonstrate a significant improvement in vascular function (doc. 4).

Also, Benowitz et al (2017) underlines that, although ECs might pose some cardiovascular risk to users, particularly those with existing cardiovascular disease, the risk is thought to be less than that of cigarette smoking based on qualitative and quantitative comparisons of EC aerosol versus cigarette smoke constituents. The adoption of ECs rather than cigarette smoking might, therefore, result in an overall benefit for public health (doc. 5).

p.15, 134: Consistently with the section on cardiovascular risks, the SCHEER opinion fails to highlight the great amount of studies that explain that e-cigarettes use is not a primary cause for carcinogenicity of the respiratory tract. Rather, Goniewicz et al (2017) for instance, shows that substituting tobacco cigarettes with an e-cigarette may reduce user exposure to numerous toxicants and carcinogens otherwise present in tobacco cigarettes (doc. 6).

Ref:

Ikonomidis et al (2020). Effects of electronic cigarette on platelet and vascular function after four months of use. <https://doi.org/10.1016/j.fct.2020.111389>.

			<p>George et al. (2019) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes Journal of the American College of Cardiology:26855 doi:10.1016/j.jacc.2019.09.067</p> <p>Benowitz et al (2017). Cardiovascular effects of electronic cigarettes. Nature Reviews Cardiology 14(8): 447–456. DOI: 10.1038/nrcardio.2017.36.</p> <p>Goniewicz ML, et al. Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. Nicotine Tob Res. 2017 Feb;19(2):160-167. doi: 10.1093/ntr/ntw160.</p>	
616	SALEMIS Philippe,C EFIC-POPG,Belgium	SCIENTIFIC OPINION	<p>0</p> <p></p> <p>PO_PG_SG_SCHEER_e-cig_opinion_comme</p>	<p>Thank you for the information. Please see reply to comment 153.</p>
617	Moiroud Jean,Fédération Interprofessionnelle de la Vape (FIVAPE), France	SCIENTIFIC OPINION	<p>P. 15, lines 5-6: “the overall weight of evidence for risk of long-term systemic effects on the cardiovascular system” is only strong for products with nicotine. The risk should be evaluated only with product with nicotine lower than 20mg/mL.</p> <p>P. 16 :</p> <p>- Lines 2-3: for second-hand exposure, the risk should be evaluated with realistic second-hand exposition. The level of PG and VG adsorption is around 90% thus only 10% is released to the ambient atmosphere. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/</p> <p>- Lines 12-13: for second-hand exposure, the risk should be evaluated with realistic second-hand exposition. The level of Nicotine adsorption is around 96% thus only 4% is released to the ambient atmosphere. See: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/</p> <p>- Lines 21-25: TSNA are only coming from tobacco extract. It is not fair to consider in the risk assessment that all e-liquids have such potential of exposure to TNSA. This concerns only e-liquids containing tobacco extract. Firstly, the levels of tobacco-specific nitrosamines in exhaled vapor are high enough that an elevated risk of cancer could not be excluded. Considering that only a very limited number of e-liquids currently on the market contain significant quantities of TSNAs, the risks associated with these</p>	<p>The SCHEER agrees, but see Table 1, answer 9.</p> <p>See answer to comment 532.</p> <p>See Table 1, answer 4.</p>

compounds can be avoided altogether by enforcing that e-liquids may not contain detectable amounts of TSNAs, in accordance with the European Tobacco Product Directive 2014/40/EU.

Moreover, Viiser et Al 2018 report that a small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids. See the report here: <https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf>

P. 17, lines 15-18: Concerning the existence of a "gateway effect" See Table 1, answer 5.

from vaping to smoking or vaping among young people. It is interesting to point out that almost all of the literature cited in this SCHEER report comes from the USA. As the authors themselves admit in p17; 115-17: "It has to be noted, that many of the studies published on this topic are dealing with data from the US. Products on the US market may differ considerably with those from the EU and conclusions drawn for the US may not be directly transferable to the EU". On this point, it is therefore regrettable that recent studies on the European market such as this one have not been taken into consideration:

<https://www.sciencedirect.com/science/article/pii/S0376871620300181>

Or the absence of certain reflections/approaches developed by Dautzenberg or Etter :

<https://onlinelibrary.wiley.com/doi/abs/10.1111/add.13924>

<https://www.sciencedirect.com/science/article/abs/pii/S0398762018307284>

P. 18:

- Lines 35-36: this statement is partially wrong. SCHEER needs to specify that this refers to the US with popular product promoted with advertisement and with nicotine content up to 59mg/mL. Other source are relevant in Europe to reconsider the gateway risk, such as:

<https://www.sciencedirect.com/science/article/pii/S0376871620300181>

Table 1 comment 5. Opinion has been adapted.

Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes. Further studies should investigate the longer-term role of vaping on future smoking habits with the use of causal inference methods. Other sources should also be considered, such as: <https://onlinelibrary.wiley.com/doi/abs/10.1111/add.13924>

- Lines 36-37: regarding nicotine, the risk should be evaluated only with product with nicotine lower than 20mg/mL.

See Table 1, answer 9.

- Lines 37-39: here are some evidence that flavours have a relevant contribution to smoking cessation: <https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

ref:

St Helen et al. (2016). Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4749433/>

Visser et al. (2015). The health risks of using e-cigarettes.

<https://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf>

Chyderiotis et al. (2020). Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France?

<https://www.sciencedirect.com/science/article/pii/S0376871620300181>

Etter J-F (2017). Gateway effects and electronic cigarettes.

<https://onlinelibrary.wiley.com/doi/abs/10.1111/add.13924>

Torregrossa H. et al. (2018). What differentiates teenage users of electronic cigarettes from users of tobacco products?

<https://www.sciencedirect.com/science/article/abs/pii/S0398762018307284>

Friedman AS, Xu S (2020). Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2766787>

Hartmann-Boyce J (2020). Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose?

https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stopsmoking-and-do-they-have-any-unwanted-effects-when-used

618 Moiroud Jean, Fédération Interprofessionnelle de la Vape
SCIENTIFIC OPINION

P. 19, lines 1-2: This statement should be re-evaluated taking in account other recent significant sources, such as: https://www.cochrane.org/CD010216/TOBACCO_can-electronic-cigarettes-help-people-stop-smoking-and-do-they-have-any-unwanted-effects-when-used

This reference was evaluated and included in the Opinion.

(FIVAPE), France		Lines 3-7: on the authors' conclusions, there is moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and compared to NRT. Evidence comparing nicotine e-cigarette with usual care/no treatment also suggests benefit but is less certain. More studies are needed to confirm the degree of effect, particularly when using modern e-cigarette products.	Please see Table 1 comment 6.
619 No agreement to disclose personal data	SCIENTIFIC OPINION	<p>p.16, 127: The data taken into consideration to support the hypothesis of a gateway role played by electronic cigarettes towards smoking among young people are partial. As a matter of fact, such data solely consider the number of users, failing to highlight the number of consumers, who, over time, have actually switched to traditional smoking products. If a gateway effect did happen, an increase of electronic cigarettes' users would go hand in hand with e-cigarettes gaining more strength in the market. However, studies and data do not show this trend. For instance, a study conducted in France on about 40,000 seventeen-year-olds found out that there is no evidence the use of the electronic cigarette subsequently led to the daily use of traditional tobacco. Furthermore, OECD data show how smoking decreased among young Europeans in the years between 2007 and 2015, when electronic cigarettes' market was well established (doc. 7 e doc. 8).</p> <p>p.17, 115: SCHEER takes into consideration many studies on the American market. This has a relevant impact on the reliability of information and the conclusion inferred, due to the key differences between the US and EU markets, both in terms of regulation and of trends among consumers. For example, the EU Directive currently in force provided for a series of specific measures for e-cigs and some Member States, namely Italy, undertook even more stringent measures in the transposition process, particularly regarding the protection of minors. As recalled at the beginning of the submission, the Italian Government decided to further address the phenomenon of initiation to smoke by allowing the sale of e-cigs exclusively through channels authorized by the competent institutions.</p> <p>P.18, 18: When it comes to e-liquids containing nicotine, it is always advisable to compare their effects with those of traditional products</p>	<p>Please see Table 1 comment 5.</p> <p>See Table 1, answer 8.</p> <p>See Table 1, answer 1.</p>

containing nicotine. In this regard, a large-scale study by the University of Pittsburgh (over 10,000 users) shows how addiction to liquid nicotine and in general to electronic cigarettes is much less strong and impactful than that of traditional cigarettes (doc. 9).

P.18, 137: SCHEER claims that flavours have a significant contribution in attracting new electronic users and, consequently, initiating to smoking products. In disagreeing with this line of reasoning, ANAFE deems appropriate to cite here a study by the university of Memphis which shows how aromas are fundamental in the process of quitting tobacco and how the ban on their sale has increased the number of smokers (doc. 10).

Ref:

Chyderiotis S, Benmarhnia T, Beck F, Spilka S, Legleye S (2020) Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? Drug and alcohol dependence 208:107853 doi:https://doi.org/10.1016/j.drugalcdep.2020.107853

OECD (2018). HEALTH AT A GLANCE: EUROPE 2018, pages 112-113

Shiffman (2020). Dependence on e-cigarettes and cigarettes in a cross-sectional study of US adults. doi: 10.1111/add.15060

Yang et al. (2020). The impact of a comprehensive tobacco product flavor ban in San Francisco among young adults. doi: 10.1016/j.abrep.2020.100273

P.18, 141: As SCHEER himself pointed out, several studies show that cessation data are largely influenced by anti-smoking policies implemented by Governments, which play a key role in the process of reducing the number of smokers. For example, Hummel et al, 2018 cited by SCHEER, shows that in England, 51.6% of those who stopped smoking used electronic cigarettes in the last quitting-attempt.

As already pointed out, ANAFE believes that the structure of the legislation currently in force (TPD Directive) allows Member States to effectively combine tax and health policies with a view to reducing the number of smokers. Following the virtuous example represented by the United Kingdom, the European Union should favour the formulation of a regulatory framework that does not limit the autonomy of Member States in the formulation of their anti-smoking policies. After all, the costs (social and non-social) of smoking are borne by national health systems, which fall under the competence of Member States under Art. 168 TFEU.

See Table 1, answer 7.

Risk management is outside the scope of the SCHEER.

620 No agreement to disclose personal data SCIENTIFIC OPINION

621	Proaño Gómez Isabel,European Federation of Allergy and Airways Diseases Patients' Organisations,Belgium	SCIENTIFIC OPINION	<p>We welcome the opportunity to comment on this preliminary opinion, as it aims to offer input to the Implementation Report of the Tobacco Products Directive 2014/40/EU , due for May next year. The report findings will in turn feed into further decisions on a possible revision of the legislation.</p> <p>There is another key reason why such initiatives are necessary: as electronic cigarettes are relatively new in the market and their share is rapidly increasing, there is an emerging need to better understand their impact on health, both from the user's and the non-user's perspective. Such an understanding requires significant commitment to longitudinal research, as well as multi-disciplinary studies to grasp the full extent of its associations with the onset and worsening of diseases such as allergy asthma and COPD.</p> <p>EFA fully relies on researchers and academics to provide input on the scientific and technical aspects of e-cigarettes. Using science as our basis, our main role as patients' representatives is to provide the patients' perspective arising from people's experiences. We firmly believe that both the scientific and the patient evidence are needed and complementary on issues affecting human health, and kindly invite SCHEER to review our contribution through this lens.</p>	Thank you for your comment.
622	Ciprian Boboi,Asociatia Industriei de Vaping (Vaping Industry Association),Romania	SCIENTIFIC OPINION	<p>n/a</p> <p>P12/ L42</p> <p>P13/ L19</p> <p>P16/ L27</p> <p>P18/L41</p> <p> Scientific_opinion.pdf</p>	See reply to comment 624.
623	Human Delon,Physician,United Kingdom	SCIENTIFIC OPINION	<p>The opinion fails to provide the crucial context of relative risk, between combustible cigarettes and e -cigarettes and the benefits derived by smokers who used these to quit smoking. An analysis of the 2017 Eurobarometer survey found that, compared to never e-cigarette use, daily e-cigarette use was associated with 5-fold higher odds of being a former smoker of ≤ 2 years and 3-fold higher odds of being a former smoker of 3-5 years. The health outcome benefit</p>	See Table 1, answer 1.

derived from this switch, both from direct and second-hand exposure, needs to be measured and recognised - as has been done in the UK

Reference: Farsalinos KE, Barbouni A. Association between electronic cigarette use and smoking cessation in the European Union in 2017: analysis of a representative sample of 13 057 Europeans from 28 countries. *Tob Control*. 2020 Feb 3;tobaccocontrol-2019-055190. doi: 10.1136/tobaccocontrol-2019-055190.

624 Ciprian Boboi, Asociatia Industriei de Vaping (Vaping Industry Association), Romania

SCIENTIFIC OPINION

Line # n/a
It is striking that throughout the report, the Committee fails to make any meaningful attempt to compare the risk of e-cigarette use to the risks of smoking. Given that, according to the Commission's own data, less than 5% of e-cigarette users are never smokers, this would seem the obvious reference point when considering the risks associated with e-cigarette use.

See Table 1, answer 1.

The report should be reframed completely regarding the risks of e-cigarettes as compared to the risks of smoking combustible cigarettes.

A good example of how this can be done is Nutt et al (2014) (*1), which systematically compares the risks of routine use of a wide range of nicotine-containing products:

“Cigarettes are the nicotine product causing by far the most harm to users and others in the world today. Attempts to switch to non-combusted sources of nicotine should be encouraged as the harms from these products are much lower.”

P 12; L 42
The hazard assessment reviews the hazard profiles of a number of substances that might be found in electronic cigarette aerosol. However, it does not compare these hazards to those found in cigarette smoke to take a view on the relative risk for each category of product. A wealth of data is available on this subject.
P 13; L 19
SCHEER notes the risk of nicotine poisoning and later (p40) states

The literature on this point was re-evaluated and the Opinion has been adapted.

that 60mg of nicotine is fatal for humans. This estimate was based on erroneous self-experiments performed in the mid of 19th century and was been corrected to 0.5-1 g several years ago (Mayer, 2014) (*2).

P 16; L 27
Stagnating or rising smoking prevalence among youth would warrant concern and should be the main indicator of a “gateway effect”. Simply put, were vaping leading more young people to smoke, then we would see a higher prevalence of smoking among young people develop as the e-cigarette came to prominence.

Please see Table 1 comment 5 and 6.

However, in the past decade, smoking rates among youth have continuously decreased at unprecedentedly high rates in virtually all EU Member States.

Data from the OECD (*3) shows that smoking among 15-16-year-olds has fallen significantly in most EU countries between 2007 and 2015, the period in which e-cigarettes were introduced onto the EU market; and data from the German Government (*4) also shows a significant fall in youth smoking rates in that jurisdiction.

P 18; L 41
The conclusion of the Committee does not take into account all of the available evidence. In addition to RCTs and cohort studies, survey data are important in measuring the effect of electronic cigarettes.

The SCHEER sufficiently underpins the conclusions in the Opinion.

Farsalinos (2016) (*5) surveyed 27.460 EU citizens from the then 28 Member States. The study concluded that E-cigarette use in the European Union appears to be largely confined to current or former smokers, while current use and nicotine use by people who have never smoked is rare. More than one-third of current e-cigarette users polled reported smoking cessation and reduction.

Observational studies should also have been considered by the Committee in respect of this question. Jackson et al (2019) (*6), for instance, concluded that “use of e-cigarettes and varenicline is associated with higher abstinence rates following a quit attempt”.

Population data can also be used to determine the rate at which e-cigarettes lead to smoking cessation. For instance, Zhu et al (2017) (*7) concluded that “The substantial increase in e-cigarette use among US adult smokers was associated with a statistically significant increase in the smoking cessation rate at the population level”.

Ref:

*1 – <https://www.karger.com/Article/Fulltext/360220>

* 2- <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/>

* 3- https://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-europe2018/smoking-among-children_health_glance_eur-2018-20-en;jsessionid=gaW_Xm7MICMouqGNEFo8IX6.ip-10-240-5-188

* 4- <https://de.statista.com/statistik/daten/studie/222992/umfrage/entwicklung-des-raucheranteilsunter-jugendlichen-in-deutschland/>

* 5- <https://pubmed.ncbi.nlm.nih.gov/27338716/>

* 6- <https://onlinelibrary.wiley.com/doi/10.1111/add.14656>

* 7- <https://www.bmj.com/content/358/bmj.j3262>

625	Gnesutta Roberto, privato, Italy	SCIENTIFIC OPINION	Page 10, line 7 - 9 SCHEER has not followed their own terms of reference - Have relied on US studies - Have not considered EU studies, for example: Chyderiotis, DKFZ, Gorini, Brozek	See Table 1, answers 2 and 8.
626	L hermet Anthont, Cigatek, France	SUMMARY	Hello, the ban on flavors or the establishment of a tax on vaping products would be a barrier to access to the only risk reduction product that really works. The price is an integral part of the motivations for quitting most smokers. The aromas help former smokers forget the taste of tobacco. By putting in place these restrictions you will simply fight against a withdrawal tool popular with millions of former smokers. we are counting on you, the vape to change our life and that of our loved ones.	Please see Table 1, answer 7. Please note that setting a 'price' is not part of the mandate.
627	No agreement to disclose personal data	SUMMARY	I quit a vapoteur and I affirm that the vape has been beneficial for me, I have not smoked for a long time thanks to the electronic cigarette, I am in great shape, whereas I was sick when I smoked real cigarettes. millions of lives could be saved by vaping.	The Opinion addresses the use and adverse health effects of electronic cigarettes, (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) . This information is important for evaluating the safety of a consumer product.

628 Da Silva Philippe, France
SUMMARY Hello, I want to clarify a certain point, the e-cigarette, it allowed me to stop smoking completely, I smoked 40 cigarettes a day, I no longer cough, I no longer have a return of mucus and when it there are some they have transparent and not brown / black, I tried the patches and the gums I smoked even more, the aromas present in the e-cigarette help to stop smoking, the fact of being able to vary the flavors and one more that avoids relapse into cigarettes, then I would like there to be more precision on the ingredients used in E-liquid. Have a nice day
Please see Table 1, answer 7.

See answer to comment no 627.

629 Mayer Bernhard-Michael, Pharmacy & Toxicology, University of Graz, Austria
SUMMARY page 6, lines 47-53 and page 8, lines 9-20
The SCHEER correctly states that nicotine intake from e-cigarettes is comparable to that of tobacco cigarettes, but appears to consider this fact a concern rather than an essential feature of these products. Sufficient nicotine delivery is indispensable for smokers' satisfaction and sustained switching without relapse back to smoking. Smokers and vapers unconsciously adjust their optimal nicotine levels [1]. When using liquids with low nicotine strength, users compensate for the lower nicotine uptake per puff by increasing daily liquid consumption [2]. Consequently, users' exposition to potentially toxic carbonyls increases with decreasing nicotine concentration of liquids [3]. Therefore, the availability of liquids with high nicotine concentration is essential for satisfaction and successful switching of smokers, particularly users of pod systems like Juul, which typically operate at a relatively low performance (~8 W).

Please see Table 1, answers 5,6,7,9.

page 7, lines 21-26
Considering that indoor air doesn't contain a significant amount of toxins (see Reply to the Abstract), there is no reason to worry about the long-term effects of second-hand exposure on cardiovascular and other health outcomes in children and adolescents. Neither adults nor underaged persons are affected by ambient air without toxins.
Please see Table 1, answer 4.

page 7, lines 38-42
Speculations about events that may happen or not in the future are not incredibly helpful for fact-based regulations. Many ingredients of liquids marketed in the US are banned in the EU, rendering the respective parts of this report irrelevant for the European
Please see Table 1, answer 8.

population.

page 7, lines 48-50
I wish to emphasize the importance of the SCHEER's statement on the increased product appeal to adults by flavors. Acceptance of e-cigarettes is essential for their benefit to public health, and the flavors are critical to their attractiveness. Unfortunately, this insight of the SCHEER is not apparent in later sections (e.g., page 8, lines 22-32), in which children and adolescents are claimed to prefer other flavors than adults. This assertion is dismissed by all available surveys, some of which were published in peer-reviewed journal articles (see, for instance, [4]).

Please see Table 1, answer 7.

page 8, lines 18-20
Public health experts and regulators, including the SCHEER and the EU commission, may wish to consider that smokers don't die from possible nicotine addiction but the inhalation of toxic tobacco smoke. Addiction without significant harm is irrelevant to public health.

Please see Table 1, answer no.5 and 6.

page 8, lines 48-53
The SCHEER questions that e-cigarettes help smokers to quit. Besides clinical studies demonstrating their effectiveness (see, for instance [5,6]), millions of testimonials to the contrary debunk this judgment as entirely wrong. E-cigarettes are not smoking cessation medicines but consumer goods serving smokers as much less harmful alternative to tobacco cigarettes. The switch from vaping to smoking is a change in behavior that must not be confused with therapeutic smoking cessation.

Please see Table 1, answer 6.

Due to limited file size, only 1 out of 6 cited papers is attached (#4).
1. Dawkins et al. Psychopharmacology (Berl) 233, 2933-2941 (2016)
2. Etter. Drug Alcohol Depend. 160, 218-221 (2016)
3. Kośmider et al. Nicotine Tob. Res. 20, 998-1003 (2018)
4. Russell et al. Harm Reduct. J. 15 (2018)
5. Hajek et al. N. Engl. J. Med. 380, 629-637 (2019)
6. Cox et al. Addict. Behav. Rep. 10, 100202 (2019)

630 No SUMMARY
agreement
to disclose

Hi I'm a french store vape seller and a customer. i 'll do my best to exprim in english what i think. There will be a shame to restreign the potential of the e-cig. it's my opinion but i think there will be

Thank you for your comment.

	personal data		many more that let down the e-cig and start smoking again. ...so how many lives saved?	
631	Boucher Philippe,th r-rendezvous .org, France	SUMMARY	Pourquoi le rapport du comité Scientifique SCHEER sur la cigarette électronique n'est-il -apparemment- disponible qu'en anglais? Et les autres langues? Idem pour la consultation citoyenne? Est-ce régulier? N'avez-vous pas une obligation de fournir des documents dans différentes langues? https://ec.europa.eu/health/scientific_committees/consultations/public_consultations/scheer_consultation_10_en	Le Secrétariat du SCHEER vous remercie pour votre message et pour l'intérêt que vous portez aux opinions de ce comité scientifique. Celui-ci est indépendant et tous les experts provenant de différents pays communiquent entre eux et rédigent en anglais. De plus, la majorité des publications utiles de la littérature sont disponibles en anglais uniquement. Leurs opinions sont donc toujours publiées officiellement dans leur langue de travail, celle qui fait foi, l'anglais. Il n'y a pas d'obligation de traduction de ces publications scientifiques. Bien à vous, Le Secrétariat du SCHEER
632	Sudenis-Miller Barbara,private person,Pol and	SUMMARY	Line numbers 13-14 Existing evidence indicates that EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical nicotine products. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/	Please see Table 1, answer 1.
633	Sudenis-Miller Barbara,private person,Pol and	SUMMARY	There is evidence of significant improvements in cardiovascular outcomes in smoking switching to e-cigarettes. TC smokers, particularly females, demonstrate significant improvement in vascular health within 1 month of switching from TC to EC. Switching from TC to EC may be considered a harm reduction measure. https://www.onlinejacc.org/content/74/25/3112	Please see Table 1, answer 1.
634	Sudenis-Miller Barbara,private person,Pol and	SUMMARY	Line numbers 13-14 Most participants experienced health benefits, mainly improvement in physical status, exercise capacity, olfactory and gustatory senses, while the most common side effects were throat irritation and cough. The strongest correlate of being a former smoker was daily e-cigarette use. Vapeshops customers in Greece are mainly current and former smokers with the majority of them having quit smoking. E-cigarette use by never smokers is rare and none of them	Please see Table 1, answers 1 and 10.

subsequently initiate smoking.
https://link.springer.com/article/10.1007/s11739-018-02011-1?fbclid=IwAR1KteVdfzEOj50KnEHT2frZMEtAmq77s_fUDb0ZQGCG_fBxOcffz-o8QF4

635 Sudenis- Miller Barbara,pri vate person,Pol and
 SUMMARY
 Line numbers 30-37
 Optimal combinations of device settings, liquid formulation and vaping behaviour normally result in e-cigarette emissions with much less carcinogenic potency than tobacco smoke, notwithstanding there are circumstances in which the cancer risks of e-cigarette emissions can escalate, sometimes substantially. These circumstances are usually avoidable when the causes are known.
https://tobaccocontrol.bmj.com/content/27/1/10?paperoc&fbclid=IwAR3UjmhQHGrdeq_ESEYfqG8d12ETWIdNNyDeOsox33aBy9HIXnbe0ZuZT8I
 Significant differences between emissions from the tested e- and conventional cigarettes are reported. Exhaled e-cigarette particles are liquid droplets evaporating rapidly; conventional cigarette smoke particles are far more stable and linger.
<https://academic.oup.com/ntr/article/21/10/1371/5040053>

Please see Table 1, answer 1 and also answer to comment no 627.

636 Sudenis- Miller Barbara,pri vate person,Pol and
 SUMMARY
 Line numbers 42-44
 “Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes”.
https://www.sciencedirect.com/science/article/pii/S0376871620300181?fbclid=IwAR2iIQx_ZKenOO9KB39OMchLpW4ImsRcHk-wwlCqEec6gxXj-zelcH3AKck
 “Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco”..
<https://academic.oup.com/ntr/article/19/11/1345/2738979>
 “These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking”.
http://beh.santepubliquefrance.fr/beh/2016/15/2016_15_2.html
 “Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect” .

Please see Table 1, answers no 5 and 6.

637 Sudenis-
Miller
Barbara, pri
vate
person, Pol
and

SUMMARY

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6652100/>
 “While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance”.
https://tobaccocontrol.bmj.com/content/28/6/629?fbclid=IwAR3vQuMwyrFa6sHDFU-jOGj82D318LXuZyUcJzT-UdWK05S-RzH8qFoeheo&utm_campaign=tc&utm_content=consumer&utm_medium=cpc&utm_source=trendmd&utm_term=usage-042019
 Line numbers 49-51
 “E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support”.
https://www.nejm.org/doi/full/10.1056/NEJMoa1808779?query=featured_home
 “Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping”.
<https://www.mdpi.com/1660-4601/14/7/798>
 The search yielded 13950 publications with 12 studies being identified as eligible for systematic review (N=8362) and 9 for random-effects meta-analyses (range: 30 to 6006 participants). The proportion of smokers achieving abstinence was 1.71 [95CI:1.02 to 2.84] times higher in nicotine EC users compared to non-nicotine EC users. The proportion of abstinent smokers was 1.69 [95CI:1.25 to 2.27] times higher in EC users compared to participants receiving NRT. EC users showed a 2.04 [95CI:0.90 to 4.64] times higher proportion of abstinent smokers in comparison with participants solely receiving counselling.
<https://pubmed.ncbi.nlm.nih.gov/32939543/>
 Current daily e-cigarette use in the EU in 2017 was rare among former smokers of >10 years and was positively associated with recent (≤ 5 years) smoking cessation. Former daily e-cigarette use was also positively associated with recent (≤ 2 years) smoking cessation.
<https://tobaccocontrol.bmj.com/content/early/2020/01/03/tobaccocontrol-2019-055190.full>

Please see Table 1, answers 6 and 7.

638 Murphy SUMMARY
Mark,Irish
Heart
Foundation
, Ireland

I wish to re-enforce the position taken by SCHEER in the summary of the preliminary opinion in e-cigarettes, supporting the findings that

1. There is moderate to strong evidence of the adverse health effects of e-cigarette use, along with moderate evidence of adverse health effects for second-hand exposed persons.
2. There is strong evidence that e-cigarettes are a gateway to smoking for young people.
3. There is weak evidence for the support of e-cigarette effectiveness in helping smokers to quit while the evidence on smoking reduction is assessed as weak to moderate.

Advocating and supporting for the position taken by SCHEER in the preliminary opinion regarding under these headings, a comprehensive review of e-cigarette studies taken by the Irish Health Research Board found as its key findings:
- E-cigarettes are no more effective than approved and regulated nicotine replacement therapies (NRTs) to help people stop smoking. However, e-cigarettes as a smoking cessation device are not regulated or approved and their safety beyond 12 months is not yet known

- Adolescents who use e-cigarettes are three to five times more likely to start smoking tobacco cigarettes compared to those who never used e-cigarettes

- E-cigarettes acute effects include poisonings, burns, blast injuries, lung injury and asthmatic attacks. Some of the chemicals in e-cigarettes are thought to cause tissue and cell damage and some are agents that may cause cancer in the long-term. The long-term health effects beyond 24 months are not researched

- Dual use of both e-cigarettes and conventional tobacco cigarettes wasn't less harmful than smoking tobacco cigarettes alone, which raises questions about the smoking reduction benefit of e-cigarettes.

It is our opinion that the SCHEER position taken in relation to e-cigarettes in terms of health harms, gateway to cigarette use, and effectiveness as a smoking cessation device is correct and reinforced by strong conclusive evidence. Our submission, backed up with evidence, supports and endorses the position taken by SCHEER.

Thank you for detailed endorsement of the Opinion.

<p>639 No agreement to disclose personal data</p>	<p>SUMMARY</p>	<p>Line numbers 13-14 „Existing evidence indicates that EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical nicotine products”. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/ „There is evidence of significant improvements in cardiovascular outcomes in smoking switching to ecigarettes”. „TC smokers, particularly females, demonstrate significant improvement in vascular health within 1 month of switching from TC to EC. Switching from TC to EC may be considered a harm reduction measure”. https://www.onlinejacc.org/content/74/25/3112</p> <p>Line numbers 13-14 „Most participants experienced health benefits, mainly improvement in physical status, exercise capacity, olfactory and gustatory senses, while the most common side effects were throat irritation and cough. The strongest correlate of being a former smoker was daily e-cigarette use. Vapeshops customers in Greece are mainly current and former smokers with the majority of them having quit smoking. E-cigarette use by never smokers is rare and none of them subsequently initiate smoking”. https://link.springer.com/.../10.1007/s11739-018-02011-1.</p> <p>Line numbers 30-37 „Optimal combinations of device settings, liquid formulation and vaping behaviour normally result in e-cigarette emissions with much less carcinogenic potency than tobacco smoke, notwithstanding there are circumstances in which the cancer risks of e-cigarette emissions can escalate, sometimes substantially. These circumstances are usually avoidable when the causes are known”. https://tobaccocontrol.bmj.com/content/27/1/10?paperoc... „Significant differences between emissions from the tested e- and conventional cigarettes are reported. Exhaled e-cigarette particles are liquid droplets evaporating rapidly; conventional cigarette smoke particles are far more stable and linger”. https://academic.oup.com/ntr/article/21/10/1371/5040053</p> <p>Line numbers 42-44 “Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes”. https://www.sciencedirect.com/.../pii/S0376871620300181... “Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco”..</p>	<p>Please see Table 1, answer 1.</p> <p>The Opinion addresses the use and adverse health effects of electronic cigarettes, (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) . This information is important for evaluating the safety of a consumer product.</p> <p>Please see Table 1, answers no 5 and 6.</p>
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<https://academic.oup.com/ntr/article/19/11/1345/2738979> “These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking”. http://beh.santepubliquefrance.fr/beh/2016/15/2016_15_2.html “Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect”. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6652100/> “While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance”. <https://tobaccocontrol.bmj.com/content/28/6/629...>

Line numbers 49-51 “E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy, when both products were accompanied by behavioral support”. <https://www.nejm.org/doi/full/10.1056/NEJMoa1808779...>

“Almost everyone (99%, 95% CI 0.96, 1.00) smoked before they started vaping. A great majority agreed that unlike with other smoking-cessation aids, they could quit smoking (81%, 95% CI 0.79, 0.90) due to vaping”. <https://www.mdpi.com/1660-4601/14/7/798> The search yielded 13950 publications with 12 studies being identified as eligible for systematic review (N=8362) and 9 for random-effects meta-analyses (range: 30 to 6006 participants). The proportion of smokers achieving abstinence was 1.71 [95CI:1.02 to 2.84] times higher in nicotine EC users compared to non-nicotine EC users. The proportion of abstinent smokers was 1.69 [95CI:1.25 to 2.27] times higher in EC users compared to participants receiving NRT. EC users showed a 2.04 [95CI:0.90 to 4.64] times higher proportion of abstinent smokers in comparison with participants solely receiving counselling. <https://pubmed.ncbi.nlm.nih.gov/32939543/> “Current daily e-cigarette use in the EU in 2017 was rare among former smokers of >10 years and was positively associated with recent (≤5 years) smoking cessation. Former daily e-cigarette use was also positively associated with recent (≤2 years) smoking cessation”. <https://tobaccocontrol.bmj.com/.../tobaccocontrol-2019...>

640 Wasik
Janusz,
Privat,
Poland

SUMMARY

Line numbers 13-14
Existing evidence indicates that EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical

Please see Table 1, answer 1.

nicotine products.
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4110871/>

There is evidence of significant improvements in cardiovascular outcomes in smoking switching to e-cigarettes. TC smokers, particularly females, demonstrate significant improvement in vascular health within 1 month of switching from TC to EC. Switching from TC to EC may be considered a harm reduction measure.
<https://www.onlinejacc.org/content/74/25/3112>

Line numbers 13-14
Most participants experienced health benefits, mainly improvement in physical status, exercise capacity, olfactory and gustatory senses, while the most common side effects were throat irritation and cough. The strongest correlate of being a former smoker was daily e-cigarette use. Vapeshops customers in Greece are mainly current and former smokers with the majority of them having quit smoking. E-cigarette use by never smokers is rare and none of them subsequently initiate smoking.
<https://link.springer.com/article/10.1007/s11739-018-02011-1>

The Opinion addresses the use and adverse health effects of electronic cigarettes, (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) .
This information is important for evaluating the safety of a consumer product.

Line numbers 30-37
Optimal combinations of device settings, liquid formulation and vaping behaviour normally result in e-cigarette emissions with much less carcinogenic potency than tobacco smoke, notwithstanding there are circumstances in which the cancer risks of e-cigarette emissions can escalate, sometimes substantially. These circumstances are usually avoidable when the causes are known.
<https://tobaccocontrol.bmj.com/content/27/1/10?paperoc...>

Please see Table 1, answers 6 and 7.

Significant differences between emissions from the tested e- and conventional cigarettes are reported. Exhaled e-cigarette particles are liquid droplets evaporating rapidly; conventional cigarette smoke particles are far more stable and linger.
<https://academic.oup.com/ntr/article/21/10/1371/5040053>

Line numbers 42-44
“Our results found no evidence of an increased risk of transitioning to daily smoking at 17 among ever-smokers who also experimented with e-cigarettes”.
<https://www.sciencedirect.com/.../pii/S0376871620300181...>

“Two-thirds of past 30-day exclusive e-cigarette users have ever used tobacco”..

<https://academic.oup.com/ntr/article/19/11/1345/2738979>

“These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking”.

http://beh.santepubliquefrance.fr/beh/2016/15/2016_15_2.html

“Data from five surveys in US/UK youths all show that, regardless of sex and age, smoking prevalence in 2014–2016 declined faster than predicted by the preceding trend, suggesting the absence of a substantial gateway effect”

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6652100/>

“While trying electronic cigarettes may causally increase smoking among some youth, the aggregate effect at the population level appears to be negligible given the reduction in smoking initiation during the period of vaping’s ascendance”.

<https://tobaccocontrol.bmj.com/content/early/2020/>

641 Martinez
Javier, JT
International
SA,
Switzerland

SUMMARY

P.6, 1.22-32 The scientific arguments advanced by the SCHEER warrant a more comprehensive critical assessment of the literature that considers and contextualizes the substantial body of literature pointing to the harm reduction potential of e-cigarettes. A landmark paper (Abrams et al. 2018) which discussed the harm minimization continuum posits that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm to exceptionally high harm. Abrams et al. point out that the potential harm of e-cigarettes falls in the low range on the continuum. By placing a greater emphasis on potential risks of e-cigarettes use, SCHHER authors fail to acknowledge that e-cigarettes may represent a major harm reduction opportunity for smokers and therefore for public health. (Beaglehole 2019)

Please See Table 1, answer 1.

P.7, 1.47 Please revise the statement that “adolescents consider flavour the most important factor trying electronic cigarettes...”

This statement is inaccurate based on the scientific studies available. The availability of flavors in e-cigarettes does not solely explain why adolescents choose to use e-cigarettes. Studies find that curiosity is the main reason among adolescents for trying e-cigarettes, with flavors coming in second or third place. In a US survey, adolescents and young adults reported curiosity as the main motivation for e-cigarettes experimentation, followed by appealing flavors and friends’ influence (Kong et al. 2015). See also Vogel et

Please see Table 1 nos 1, 5, 6 and 7.

al. 2019. Please revise this statement to be consistent with the scientific literature and in line with SCHEER's statement page 7, line 32, "Amongst young adults, curiosity was the most frequently reported reason for initiating the use of electronic cigarettes."

P.8, 1.22-23 Please revise the statement, "Some data available from the US indicate that the prevalence of electronic cigarette use is increasing in children and adolescents." More recent data report a decline in current e-cigarette use among US adolescents between 2019 and 2020 (Wang. 2020). Please caution that conclusions drawn for the US may not be directly transferable to the EU because products on the US market differ considerably from those sold in the EU, and US and EU have different regulations.

Please see table 1, answer. 8.

P.8, 1.28-29 Please revise the statement: "there is strong evidence that electronic cigarettes are a gateway to smoking for young people." SCHEER interpretation of the evidence to support and qualify that vaping serves as a "strong" gateway to smoking is not sound. Based on the scientific studies available and national smoking prevalence data in Member States, the evidence should not be qualified and reported as "strong". Please refer to our extensive comment and additional scientific studies provided in relation to P.67, 1.26 onwards. Please amend this statement.

Please see Table 1, answer 5.

P.8, 1.52-53 Please revise the statement "Taking into account data from cohort studies and randomised control trials, the weight of evidence for smoking cessation is weak to moderate..." Based on the scientific literature available, the evidence should not be reported as "weak". The most recent Cochrane Review document contradicts SCHEER conclusion, pointing out, "we now find moderate-certainty evidence of benefit when comparing nicotine EC with NRT" See Hartmann-Boyce et al. 2020. The review concludes, "Nicotine e-cigarettes probably do help people to stop smoking for at least six months" adding, "None of the included studies (short- to mid-term, up to two years) detected serious adverse events considered possibly related to EC use." Please also refer to our extensive comments and additional scientific studies provided under section 6.7 Role of electronic cigarettes in the

The SCHEER has sufficiently underpinned the conclusions in the Opinion.

			cessation of traditional tobacco smoking and dual use, P.70, 1.19-28	
642	Landl Michael, World Vapers' Alliance, Austria	SUMMARY	<p>Page 7, Lines 16 - 19: Vaping has been proven to be 95% less harmful than smoking [1] and has been endorsed by multiple international health bodies as a safer alternative.</p> <p>Page 7, Lines 38-42: This seems to be very speculative, because many ingredients in liquids in the US are banned in the EU. On this false basis, many following arguments in the report seem to be irrelevant.</p> <p>Page 7, Lines 44-50: This argument does not seem to align with the experience of actual vapers. According to the Drug Strategy Household Survey [2] in Australia, the majority of adults (54%) (and even more young adults with 72%) try vaping out of curiosity, while vaping for taste was ranked last in the reasons people vaped. In the United States, the PATH study [3] and the CDC [4] found very similar patterns. To the contrary, survey results from the longitudinal survey study from Yale School of Public Health [5] found that “relative to vaping tobacco flavors, vaping non tobacco-flavored e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation”.</p> <p>Page 8, Line 28 - 32: A closer look at the outcome of the survey shows that only 2,1% of non-smoking [6] individuals surveyed frequently used e-cigarettes. The data from Action on Smoking and Health (ASH) UK [7] reports similar findings and states that youth smoking rates are at an all-time low and youth use of e-cigarettes is rare, and most users are current or former smokers. E-cigarettes are less appealing to adolescents than many believe.</p> <p>Page 8, Line 48-53: Apart from millions of vapers, who were able to quit smoking thanks to e-cigarettes, studies do show the effectiveness of vaping as a cessation tool. Vaping is twice as effective as nicotine replacement therapies. [8][9] References: [1] McNeill A, Brose LS, Calder R, Hitchman SC, E-cigarettes: an evidence update, A report commissioned by Public Health England [2] AIHW, National Drug Strategy Household Survey 2019</p>	<p>Please see Table 1, answer 1.</p> <p>Table 1, answer 8.</p> <p>Table 1, answers 5 and 7.</p>

[3] Nicksic NE, Snell LM, Barnes AJ. Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study. *Addict Behav.* 2019;93:93-99. doi:10.1016/j.addbeh.2019.01.037

[4] Wang TW, Gentzke AS, Creamer MR, et al. Tobacco Product Use and Associated Factors Among Middle and High School Students —United States, 2019. *MMWR Surveill Summ* 2019;68(No. SS-12):1–22

[5] Friedman AS, Xu S. Associations of Flavored e-Cigarette Uptake With Subsequent Smoking Initiation and Cessation. *JAMA Netw Open.* 2020

[6] Martin Jarvis, Sarah Jackson, Robert West, Jamie Brown. (2020). Epidemic of youth nicotine addiction? What does the National Youth Tobacco Survey 2017-2019 reveal about high school e-cigarette use in the USA?.

[7] Action on Smoking and Health, New ASH data reveals that youth use of e-cigarettes in Great Britain is very low

[8] [9] A randomised trial of e-cigarettes versus nicotine replacement therapy'. Peter Hajek, PhD, Anna Phillips-Waller, BSc, Dunja Przulj, PhD, Francesca Pesola, PhD, Katie Myers Smith, DPsych, Natalie Bisal, MSc, Jinshuo Li, MPhil, Steve Parrott, MSc, Peter Sasieni, PhD, Lynne Dawkins, PhD, Louise. Ross, Maciej Goniewicz, PhD, PharmD, Qi Wu, MSc, Hayden James McRobbie, PhD. *New England Journal of Medicine.*

643	Bates Clive, Counterfactual Consulting Limited, United Kingdom	SUMMARY	<p>The primary failure of the SCHEER preliminary scientific opinion as summarised in this section is that it does not provide a scientific analysis that is useful to policymakers considering the effect of the Tobacco Products Directive and whether a future revision is necessary. In its current preliminary form, it is not fit for purpose.</p> <p>The following eleven concerns are evident and detailed in the attachment:</p> <ol style="list-style-type: none"> 1. Inadequate comparison with cigarettes: the principal public health value of e-cigarettes is as a low-risk alternative to cigarettes. 2. Inadequate comparisons with other benchmarks: there are exposures to toxins associated with e-cigarette use, but SCHEER does compare these to realistic benchmarks of absolute tolerability of risk, such as occupational health exposure standards. 3. Inadequate quantification of risk: it is of no value to report a hypothetical risk, such as the presence of a hazardous agent, without asking whether this is 'material'. 4. Poor differentiation between observable effects and markers for risk: nicotine use and vaping cause several observable effects on the body but it leaps to unjustified conclusions that such effects are markers for harms, but they are not. 5. Overstating evidence on secondhand vapour: there is no evidence supporting a plausible risk from exposure to secondhand vapour and good reasons to believe any risk will be negligible. These 	<ol style="list-style-type: none"> 1. Please see Table 1, answer 1. 2. Please see Table 1, answer 3. 3. Please see Table 1, answer 3. 4. The SCHEER uses the internationally accepted procedures for risk assessment. 5. Please see Table 1, answer 4.
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reasons include the low toxicity of vapour, the much smaller volumes produced compared to smoking and rapid dispersal in the atmosphere.

6. Misunderstanding the public health mechanism of vaping: the report simplistically expresses concern that vaping might be appealing, yet that is how it works to attract smokers away from smoking.

7. Overplaying uncertainty over the long term: there is much less uncertainty than SCHEER suggests, given what we already know of vapour toxicity and human biomarkers of exposure.

8. Misunderstanding basic epidemiological concepts regarding the gateway effect: the report makes trivial errors with a failure to recognise the challenges of confounding and "common liability" as an explanation for associations between smoking and vaping.

9. Ignoring and selectively interpreting evidence: SCHEER has selectively reported and interpreted evidence concerning smoking cessation, ignoring compelling evidence that vaping displaces smoking.

10. Shifting and raising evidential hurdles: SCHEER demands evidence for e-cigarettes that are not routinely applied to standard smoking cessation methods.

11. The complete absence of policy impact research: the most serious failing is the omission of scientific research related to the effect of policies on smoking and vaping behaviour. Policy impact research is the most critical science for policymakers, and it is wholly absent from the preliminary opinion.

To assist the Committee's efforts to improve the final report, I have detailed these concerns on my blog [1]. I intend to produce a detailed critique of the final opinion to assist decision-makers and influential stakeholders in the European Parliament, European Council working group, the European Commission and relevant stakeholders. I hope that by then, SCHEER will have addressed most or all of these concerns and produced an opinion that provides a useful and objective assessment that assists policymakers.

[1] Bates, CD. European Commission SCHEER scientific opinion on e-cigarettes - a guide for policymakers, The Counterfactual, 30 September 2020. <https://www.clivebates.com/european-commission-scheer-scientific-opinion-on-e-cigarettes-a-guide-for-policymakers> [and uploaded attached]

6. Please see Table 1, answers 1, 5, 6 and 7.

7. The SCHEER used the criteria described in its Guidance on weight of evidence.

8. Please see Table 1, answers 5, 6 and 7.

9. The SCHEER used the criteria described in its Guidance on weight of evidence.

10. The SCHEER used the criteria described in its Guidance on weight of evidence.

11. the impact on policy is outside of the scope of this Opinion.

644	Ross Louise, National Centre for Smoking Cessation and Training (NCSCT - England), United Kingdom	SUMMARY	49-52 My comments on this section are based on clinical experience. I launched the first e-cigarette-friendly Stop Smoking Service (SSS) in England in 2014, and from the first Quarter's results we could see that vaping was a more successful method of stopping smoking than nicotine replacement therapy or Varenicline. Those who stopped with vaping were around 20% more likely to quit successfully than those who used more traditional methods. They were typically people who had tried quitting many times before, and described their experience with vaping as a revelation. We saw consistent patterns as the years went on, and since our modest start on being vape-friendly in 2014, many other SSSs have chosen the same approach, with equal success. Your report threatens to deter people from switching, and this will ultimately keep them smoking.	See Table 1, answer 1. The Opinion addresses the use and adverse health effects of electronic cigarettes, (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) . This information is important for evaluating the safety of a consumer product.
645	No agreement to disclose personal data	SUMMARY	I DO NOT AGREE WITH THE REPORT SCHEER	Thank you for your comment.
646	No agreement to disclose personal data	SUMMARY	Page 6 Line 34: THE OPINION DOES NOT CONSIDER HOW LEVELS OF CHEMICALS IN E-CIGARETTE AEROSOLS COMPARE TO CIGARETTE SMOKE Aerosol chemistry studies have shown e-cigarette aerosols contain fewer and substantially lower levels of harmful chemicals compared to cigarette smoke.[1] Moreover, a growing body of clinical data has shown that adult smokers who transition to e-cigarettes have substantially lower exposure to carcinogens and toxicants compared to cigarette smoking, with reductions largely indistinguishable from complete smoking cessation or use of licensed Nicotine replacement Therapy (NRT) products.[2] These studies are absent from the SCHEER Opinion. P8 L46: E-CIGARETTES ARE MORE EFFECTIVE THAN NRT FOR ADULT SMOKERS TO REDUCE AND REPLACE CIGARETTE SMOKING The 2020 Cochrane Review,[3] which evaluated the effect and safety of using e-cigarettes to help smokers achieve long-term smoking abstinence, and considered 50 studies in 12,430 adults (studies that took place in the USA (21 studies), the UK (9), Italy	Please see Table 1, answer 1. Please see Table 1, answer 6. Please see Table 1, answer 11.

(7), Australia (2), New Zealand (2), Greece (2), and one study each in Belgium, Canada, Poland, South Korea, South Africa, Switzerland and Turkey), concluded nicotine-containing e-cigarettes: [i] do help people to stop smoking (even amongst those who do not intend to quit smoking) and work better than NRT and nicotine-free e-cigarettes; [ii] are better for smoking cessation than no support, or behavioural support alone; [iii] and are not associated with serious unwanted effects or harm with up to two years product use. Given Cochrane Reviews are internationally recognised as the gold standard of scientific evidence, the 2020 Cochrane Review should be considered by SCHEER before finalising its opinion.

Outside of randomised control clinical settings extensively presented in the Cochrane Review, real-world data has shown that over 6.1 million adult smokers quit smoking using e-cigarettes in the EU, while another 9.2 million had significantly reduced their cigarette consumption[4]. A recent EU study also showed current daily e-cigarette use was rare among former smokers and was positively associated with recent smoking cessation[5]. Consistent with this, an analysis of Eurobarometer survey data also showed the while the use of medically licensed pharmacotherapy have become less popular, use of e-cigarettes for smoking cessation has increased substantially from 3.7% in 2012 to 9.7% in 2017[6].

In considering the effectiveness of e-cigarettes in smoking cessation, SCHEER should also ascertain how different Member States' regulatory environments may influence this. A recent study found the use of e-cigarettes in the real-world is only effective for sustaining smoking absence in a less restrictive e-cigarette environment and the benefits of e-cigarettes for population-level tobacco harm reduction are highly dependent on the regulatory environment[7]. Thus, it is not surprising the UK now has one of the lowest smoking rates in Europe given their pragmatic approach to the regulation of e-cigarettes via EUTPD, coupled with regulatory and public health endorsement of the category as a tool for smoking cessation.

Please see Table 1, answers 1 and 6.



Summary.pdf

647	Chaplia Maria,Con sumer Choice Center,Uni ted States	SUMMARY	<p>Page 7, LINE 16 - 19: The U.K.’s top health body, Public Health England, has repeatedly said that vaping and e-cigarettes are 95 per cent less harmful than smoking. The same conclusion has been drawn by the New Zealand Ministry of Health and Health Canada, which have both launched public initiatives imploring smokers to turn to vaping.</p>	Please see Table 1, answer 1.
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<p>Page 7, LINE 38-42: Many ingredients in liquids in the US are banned in the EU. Therefore, many of the following arguments in the report seem to be irrelevant.</p>	This issue is already discussed in the Opinion.
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<p>Page 7, LINE 44-50: Flavours play a key role in helping smokers quit. Legislation on vaping flavours must take this fact into account. A study published in the New England Journal of Medicine in 2019 assigned participants into e-cigarettes and nicotine replacement groups and found that vaping was twice as effective as nicotine-replacement products in helping smokers quit. Crucially, participants in the e-cigarette group were encouraged to experiment with e-liquids of different strengths and flavours. Among participants in the study who didn’t fully stop smoking, those in the e-cigarette group were more likely to reduce their smoke intake than those in the nicotine-replacement group. Survey results from the longitudinal survey study from Yale School of Public Health found that “relative to vaping tobacco flavours, vaping non-tobacco-flavoured e-cigarettes was not associated with increased youth smoking initiation but was associated with an increase in the odds of adult smoking cessation”.</p>	Please see Table 1, answers 1 and 7.
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<p>Page 8, Line 28 - 32: Nicotine, also found in e-cigarettes and used in conventional nicotine replacement therapy, doesn’t increase the risk of serious illnesses (heart attack, stroke) or mortality. The British National Health Service sticks to the following view: “While nicotine is the addictive substance in cigarettes, it’s relatively harmless. Almost all of the harm from smoking comes from the thousands of other chemicals in tobacco smoke, many of</p>	Please see the answers to the specific chapters.
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which are toxic.

A closer look at the outcome of the survey shows that only 2,1% of non-smoking individuals surveyed frequently used e-cigarettes. The Action on Smoking and Health (ASH) UK reports similar findings and states that youth smoking rates are at an all-time low and youth use of e-cigarettes is rare, and most users are current or former smokers.

Page 8, Line 48-53: The effectiveness of e-cigarettes as a smoking cessation tool is undeniable, keeping in mind that it targets smokers as opposed to non-smokers. Vaping is twice as effective as nicotine replacement therapies.

648 Vejdovszky Katharina, AGES - Austrian Agency for Health and Food Safety, Austria

SUMMARY

Page 6, lines 37-38
It stated that e-liquids mainly comprise of propylene glycol, glycerol, nicotine, water, flavourings and preservatives. However, there is no common definition of an “e-liquid” regarding its ingredients, neither in the Directive 2014/40/EU, nor elsewhere. In fact, there are products available, which contain e.g. a considerable amount of oils (MCT) as main carrier. Health issues associated with oil as carrier are incomparably higher than those associated with propylene glycol or glycerol.

We believe that such issues which involve major health hazards should be included in an opinion on electronic cigarettes, especially when authored by a scientific committee of the European Commission. The topic of e-liquids consisting of other carriers than propylene glycol and glycerol, however, was disregarded in this opinion.

Page 6, lines 34-45
It stated that chemicals in e-cigarette aerosol can have different origin e.g.: i) from e-liquids (propylene glycol, glycerol, nicotine, water, flavourings, preservatives). However, we are of the opinion that contaminants should be added to this list, as they could potentially pose health risks. Furthermore, a data collection of contaminants in e-liquids and an evaluation of associated risks would be of high value to enable regulatory measures.

The SCHEER focusses this Opinion on the most frequent chemicals originally used in e-liquids and others that may be generated by chemical reactions through heating of the e-liquid and/or the device itself and to which users of electronic cigarettes may be exposed to through the inhaled aerosol.

The SCHEER is aware that the list of chemicals evaluated is not exhaustive.

			Page		lines	
			8,		8-20	
			We think that, besides the nicotine content itself, the issue of pH in the aerosol and the associated systemic delivery of nicotine plays a pivotal role and should be mentioned.			Thank you for your comment.
649	Wyszynsk a-Szulc Agnieszka, Philip Morris Products S.A., Switzerlan d	SUMMARY	P.	7	1.	16-18
			The SCHEER's Opinion omits to mention the relative health risk of e-cigarettes' use compared to continuing smoking. There is a large body of evidence demonstrating that e-cigarettes are less harmful compared to continued smoking and we recommend to add such conclusion to the opinion, including the here referenced publications (U.K.'s Royal College of Physicians 2007; U.K.'s Royal College of Physicians 2016; McNeill 2015; COT 2020; DKFZ 2020).			Please see Table 1, answer 1.
			P.	7	1.	57
			McNeill (2020) raises valid concerns about risks of unintended consequences to smokers regarding potential flavour bans, which we suggest to be added on p.7 l. 57.			Please see the answers to the specific chapters.
			We suggest also to add the relevant findings from Romijnders (2019) and Leventhal (2019) on the need for a balanced approach to regulation of flavours on p.8 l.1.			
			P.	8	1.	22-23
			Based on ASH UK (2020), Wang (2020) and McNeill (2020), we recommend to revise p. 8 l. 22-23 and include the following: "However, the recent data from the UK, where e-cigarettes' use is widespread, show that regular e-cigarettes' use among youth is low, while the latest US survey shows a declining trend within this population."			
			P.	8	1.	28-32
			We suggest that the SCHEER reconsiders the weight afforded to the available evidence. Several studies from EU countries, which were omitted in the Opinion, dismiss the gateway theory, while the theory itself is being largely questioned by public health experts (e.g. Public Health England (McNeill 2015) and Etter 2018). Therefore, there is no substantiation to describe the weight of evidence as strong and we recommend to change the conclusions in			

the SCHEER's opinion in line with this evidence which we reference in our comments to Section 6.6.

P. 8 1. 48-53

The SCHEER's Opinion omits several recent studies, relevant for EU, that demonstrate the effectiveness of nicotine containing e-cigarettes in smoking cessation. We believe that consideration of the studies cited in our comment to Section 6.7 may impact the SCHEER's determination that there is weak evidence on the effectiveness of e-cigarettes in smoking cessation and that evidence on smoking reduction is moderate to weak. Therefore, we suggest omitting on p. 8 1.48-53 and adapting the conclusions according to the evidence which we quote in Section 6.7. It is worth also including in the opinion the recent practice of the cessation services in some European countries. For example, the national health agency Santé Publique France and the UK National Health Services acknowledge the role of e-cigarettes in cessation and smoking reduction, and recommend (e.g. via their websites) switching to e-cigarettes as one of the ways for smoking cessation.

This Section also omits the important role flavours can play in helping smokers quit smoking. The studies cited in our comment to Section 6.6 concluded that non-tobacco flavours and non-menthol flavours, especially fruit flavours, facilitate the switching of smokers compared to traditional tobacco and menthol flavours. We suggest the following be added to p.8 1.54 "Several studies demonstrate that non-tobacco flavoured and non-menthol flavoured, especially fruit flavoured e-liquids, facilitate the switching of smokers compared to traditional tobacco and menthol flavoured e-cigarettes (Romijnders (2019); Du (2020), Russel (2018), Gravely (2020), Friedman (2020), Havermans (2019))."



ref-649.docx

650	O'Leary Renee, Cen ter of Excellence	SUMMARY	P6L17-18 Alternative hypotheses to a gateway effect for the association of youth use of ENDS and cigarettes must be considered, including common liabilities.	Please see Table 1, answer 1.
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for the
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on of
Harm
Reduction,
University
of Catania,
Italy,Italy

P6L47-53 Not all ENDS use involves consuming nicotine liquids. Please see the answers to the specific chapters.

P6L57, P7L21-26 Second-hand exposures should be evaluated against known occupational standards.

P7L16-19 The relative harm of ENDS use must be weighed against the harms of continued smoking. Evidence from clinical studies shows improvements in health by persons who substitute ENDS use for smoking.

P7L28-29, P7L38-42 Recent data are scarce on trends in EU youth use of ENDS. The ESPAD report 2020, the European School Survey Project on Alcohol and Other Drugs, is due out November 12, 2020. A substantial number of EU youth reporting ever-use experimented on only one occasion. Many EU youth do not use nicotine. Data are available on EU youth use; this evidence should be prioritized over US and other non-EU studies.

P7L44-50 While flavours are attractive to youth and adults, curiosity is by far the major reason to try ENDS. Evidence shows that the use of flavours by US youth has no effect on their rates of smoking initiation. Flavour use has been shown to increase cessation efficacy in US adults.

P8L28-29 The evidence is mixed on a gateway effect based on data in two large survey datasets, one of which was conducted in France.

P8L48-53 The recently published Cochrane review (Hartmann-Boyce et al., 2020) concludes there is moderate-certainty evidence that ENDS use for cessation results in a higher quit rate than nicotine replacement therapy (NRT). Evidence from longitudinal and cross-sectional studies, and a report from Belgium on ENDS use in tobacco treatment demonstrates that ENDS are beneficial for cessation.

P8L55 “The available evidence indicates a possible positive effect of ENDS on population health, particularly if appropriate ENDS regulation is enacted to maximize their benefits and minimize their risks.” WHO Study Group on Tobacco Product Regulation, Report

651	Pietsch Franz, Austrian Federal Ministry of Social, Health, Care and Consumer Protection, Austria	SUMMARY	<p>on the Scientific Basis of Tobacco Product Regulation: Seventh Report of a WHO Study Group, 2019, p. 60.</p> <p>The Austrian MoH sees the SCHEER report as a valuable and helpful interim assessment of the progressive e-cigarette consumption that has been relevant since almost 10 years, without taking into account any long-term effects or benefits.</p> <p>In general the Austrian MoH agrees with the results of the SCHEER-report which raises awareness and contributes to the development and implementation of strategies regarding legal based regulations on a national level taking into account all kinds of emerging tobacco products and its respective health policies.</p> <p>From the MoH's point of view preventing entry is the best prevention, which moreover does not require a later switch. E-cigarettes and tobacco heaters represent a mere continuation of the same nicotine consumption, but with a different modality (= switch).</p> <p>E-cigarettes and tobacco heaters undoubtedly close a gap in nicotine replacement products because, unlike nasal, oral and dermal nicotine products (such as chewing gum, sprays or tablets, etc.), they are not available as inhaled products. However, unlike nicotine replacement products, they are not clinically tested for harm reduction consumer goods at all. In this context, the justification of e-cigarette use as part of a harm reduction program is misleading and inadmissible; there is a lack of evidence-based studies concerning consumption and its long-term effects as well as real added values or cessation benefits .</p> <p>Some stakeholders underlined some aspects of the methodology of the SCHEER-report, such as the disproportionality concerning the depth and outcome of investigation of the gateway-effects in relation to smoking cessation.</p>	Thank you for your comments.
652	Vape Business Ireland Vape Business	SUMMARY	<p>The SCHEER opinion dismisses the fact that vaping products are commonly used as less harmful alternatives to smoking. A fundamental acknowledgement of the difference in comparative risk between vaping products and combustible cigarettes is entirely absent in this opinion. In particular, that vaping products are a less</p>	Please see Table 1, answer 1.

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harmful alternative to smoking and switching can significantly reduce a smoker's exposure to the harmful toxicants found in cigarette smoke. A 2015 expert independent evidence review, E-cigarettes: an evidence update, published by Public Health England concluded that vaping products are significantly less harmful to health than tobacco and have the potential to help smokers quit smoking, estimating that vaping is around 95% less harmful than smoking

The 2017 European Commission Special Eurobarometer 458 on Attitudes of Europeans towards tobacco and electronic cigarettes shows 26 per cent of EU citizens' smoke. They are at most serious risk of disease and premature death, with 700,000 of them dying each year. If the Commission is serious about reducing smoking prevalence, then acknowledging the positive public health role that vaping products could play in a healthier Europe is fundamental to making that plan a success.

653 Muntadas- SUMMARY Page 6. Lines 47-53

Prim
Ángeles, A
NESVAP,
Spain

Comment
Nicotine self-titration is key to avoid craving and maintain people smoke-free. It is the bio-mechanism that ensures vapers and smokers to not be poisoned while vaping or smoking. The SCHEER considers nicotine consumption as unacceptable for smokers and electronic cigarettes users while it is well accepted for NRTs even when administered in combination at high concentrations.

References:

Farsalinos K, Poulas K, Voudris V. Changes in Puffing Topography and Nicotine Consumption Depending on the Power Setting of Electronic Cigarettes. *Nicotine Tob Res.* 2018 Jul 9;20(8):993-997. doi: 10.1093/ntr/ntx219. PMID: 29059377; <https://pubmed.ncbi.nlm.nih.gov/29059377/>
Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced ecigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl).* 2016 Aug;233(15-16):2933-41. doi: 10.1007/s00213-016-4338-2. Epub 2016 May 27. PMID: 27235016. <https://pubmed.ncbi.nlm.nih.gov/27235016/>
Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. *CNS Drugs.* 2001;15(6):453-67. doi: 10.2165/00023210-200115060-00004. PMID: 11524024. <https://pubmed.ncbi.nlm.nih.gov/11524024/>

The Opinion addresses the use and adverse health effects of electronic cigarettes, (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) .
This information is important for evaluating the safety of a consumer product
NRT is therapy which comes under pharmaceutical regulation.

654	Muntadas-Prim Ángeles,A NESVAP, Spain	SUMMARY	<p>Page 7. Lines 4-8</p> <p>Comment</p> <p>We suppose that SCHEER is referring to flavours as “other chemicals”. The vast majority of flavouring compounds in e-cigarette liquids are present at far lower levels than those required to classify them as toxic.</p> <p>Ref: Farsalinos K, Lagoumintzis G. Toxicity classification of e-cigarette flavouring compounds based on European Union regulation: analysis of findings from a recent study. Harm Reduct J. 2019 Jul 25;16(1):48. doi: 10.1186/s12954-019-0318-2. PMID: 31345235; PMCID: PMC6659232. https://pubmed.ncbi.nlm.nih.gov/31345235</p>	<p>Flavourings are used for a specific effect. Please see Table 1, answer 7.</p>
655	Muntadas-Prim Ángeles, ANESVA P, Spain	SUMMARY	<p>Page 7. Lines 10-14</p> <p>Comment</p> <p>There are many references to explosions by lithium batteries in different devices and poisonings by common household substances. Nevertheless SCHEER should consider that the relevant comparator is fires and related injuries caused by smoking materials – there is around three orders of magnitude difference. For example, according to the US National Fire Protection Association, around 18,000 fires were caused annually in the US by smoking materials from 2012-16.</p> <p> ref-655.docx</p>	<p>Thank you for the information.</p>
656	Muntadas-Prim Ángeles,A NESVAP, Spain	SUMMARY	<p>Page 7. Lines 16-19</p> <p>Comment</p> <p>The SCHEER should consider what is better or less harmful for the cardiovascular health of smokers: should they continue smoking or should they switch to vaping? In the report there is no comparison between the CV effects of smoking compared to vaping.</p> <p>Ref: Jacob George, Muhammad Hussain, Thenmalar Vadiveloo, Sheila Ireland, Pippa Hopkinson, Allan D. Struthers, Peter T. Donnan, Faisal Khan, Chim C. Lang. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic CigarettesJ Am Coll Cardiol. 2019 Dec, 74 (25) 3112-3120.https://www.onlinejacc.org/content/74/25/3112</p>	<p>Please see Table 1, answers 1 and 11.</p>
657	Muntadas-Prim Ángeles,A	SUMMARY	<p>Page 7-8. Lines 44-13</p> <p>Comment</p> <p>The attractiveness of flavors and the efficiency in delivering</p>	

	NESVAP, Spain		nicotine are absolutely critical factors in the effectiveness of e-cigarettes for smoking cessation. Keeping non-smoking minors away from these products is something that must be achieved through regulation, but the health of millions of adult smokers cannot be sacrificed. Ref: Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Prevalence and correlates of current daily use of electronic cigarettes in the European Union: analysis of the 2014 Eurobarometer survey. Intern Emerg Med. 2017 Sep;12(6):757-763. doi: 10.1007/s11739-017-1643-7. Epub 2017 Mar 4. PMID: 28260221. https://pubmed.ncbi.nlm.nih.gov/28260221/ Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. Int J Environ Res Public Health. 2013 Dec 17;10(12):7272-82. doi: 10.3390/ijerph10127272. PMID: 24351746; PMCID: PMC3881166. https://pubmed.ncbi.nlm.nih.gov/24351746/ Russell, C., McKeganey, N., Dickson, T. et al. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. Harm Reduct J 15, 33 (2018). https://doi.org/10.1186/s12954-018-0238-6 https://harmreductionjournal.biomedcentral.com/articles/10.1186/s12954-018-0238-6 Farsalinos et al. Patterns of flavored e-cigarette use among adults vapers in the United States: an internet survey. Submitted to: Docket No. FDA-2017-N-6565 for "Regulation of Flavors in Tobacco Products." https://vitaofcanada.com/resources/patterns-of-flavored-e-cigarette-use-among-adults-vapers-in-the-united-states-an-internet-survey/	Please see Table 1, answers 5 and 7.
658	Muntadas-Prim Ángeles,A NESVAP, Spain	SUMMARY	Page 8. Lines 34-46 Comment The SCHEER should analyze how misinformation about electronic cigarettes could negatively influence the number of quitting smoking attempts. Misinformation and misperceptions cause smokers to not try vaping and continue to smoke. Ref: Martin Dockrell. GOV.UK. Public Health Matters. Clearing up some myths around e-cigarettes. 2018. https://publichealthmatters.blog.gov.uk/2018/02/20/clearing-up-some-myths-around-ecigarettes/ PHE. Research and analysis. Vaping in England: 2020 evidence update summary. Published 4 March 2020 https://www.gov.uk/government/publications/vaping-in-england-evidence-update-march2020/vaping-in-england-2020-evidence-update-summary	Please see Table 1, answer 1.
659	Ribes Arturo,UP EV,Spain	SUMMARY	Page 6. Lines 47-53 Comment: Nicotine self-titration in electronic cigarettes mean an opportunity for users to gradually reduce the dependency from nicotine until it can progressively abandon its needed dose. Contrary to other nicotine replacement therapies, with electronic	See Table 1, answer 9. Nicotine replacement therapies are outside of the scope of the Opinion.

cigarettes this is a real possibility which cannot be provided to nicotine consumers in any other way or mean. It is regrettable to see that the SCHEER accepts nicotine consumption in nicotine replacement therapies but oversees electronic cigarettes as nicotine consumption replacement products.

Ref:

Farsalinos K, Poulas K, Voudris V. Changes in Puffing Topography and Nicotine Consumption Depending on the Power Setting of Electronic Cigarettes. *Nicotine Tob Res.* 2018 Jul 9;20(8):993-997. doi: 10.1093/ntr/ntx219. PMID: 29059377.

<https://pubmed.ncbi.nlm.nih.gov/29059377/>

Dawkins LE, Kimber CF, Doig M, Feyerabend C, Corcoran O. Self-titration by experienced e-cigarette users: blood nicotine delivery and subjective effects. *Psychopharmacology (Berl)*. 2016 Aug;233(15-16):2933-41. doi: 10.1007/s00213-0164338-2. Epub 2016 May 27. PMID: 27235016.

<https://pubmed.ncbi.nlm.nih.gov/27235016/>

Sweeney CT, Fant RV, Fagerstrom KO, McGovern JF, Henningfield JE. Combination nicotine replacement therapy for smoking cessation: rationale, efficacy and tolerability. *CNS Drugs*. 2001;15(6):453-67. doi: 10.2165/00023210-200115060-00004. PMID: 11524024. <https://pubmed.ncbi.nlm.nih.gov/11524024/>

660	Ribes Arturo, UPEV, Spain	SUMMARY	Page 7.	Lines 10-14
			Comment: The security of electronic cigarettes batteries is guaranteed by the EU standards created under the EU batteries directive and ROHS. Therefore, even if the SCHEER considers batteries explosion in third countries, it is overlooking that the CE marking provides a safety stamp in consumers products under the strictest rules worldwide for manufacturing, market placement and disposal of batteries. The SCHEER is therefore not analyzing a European problem.	
661	Ribes Arturo, UP EV, Spain	SUMMARY	Page 7-8.	Lines 44-13
			Comment: Flavors cannot be considered as a focal problem of attractiveness to consumers but as an asset to move people away from smoking. The possibility to attract smokers to a much lower risk mean of consuming nicotine is in most of the cases done through attractive flavors which are nothing like tobacco flavor. In fact, it is flavors what increases the distance between tobacco and vapor products. Minors cannot access to these products if the regulations work by setting a proper age of purchasing and controls are being put in place.	
662	Ribes Arturo, UP EV, Spain	SUMMARY	Page 8.	Lines 34-46
			Comment: Not providing proper information as regards the different risk profile of e-cigarettes and traditional tobacco is	

The SCHEER disagees, data from RAPEX were used.

See Table 1, answer 7.

Please see Table 1, answer 1.

preventing millions of smokers to quit smoking as they perceive that any alternative is as harmful for their health as tobacco. Appropriate campaigns should be put in place to help people quit smoking by changing to safer options like the one recently published in France or the UK.

Ref:

Santé Publique France. J'arrête de fumer, Je choisis la cigarette électronique. Published October 2020. <https://www.tabac-info-service.fr/j-arrete-de-fumer/je-choisis-la-cigarette-electronique>

Martin Dockrell. GOV.UK. Public Health Matters. Clearing up some myths around ecigarettes. 2018.

<https://publichealthmatters.blog.gov.uk/2018/02/20/clearing-up-some-myths-around-ecigarettes/>

PHE. Research and analysis. Vaping in England: 2020 evidence update summary. Published 4 March 2020

<https://www.gov.uk/government/publications/vaping-in-england-evidence-updatemarch-2020/vaping-in-england-2020-evidence-update-summary>

663 Arffman
Päivi, Vapers
Finland, Finland

SUMMARY

”Some data available from the US indicate that the prevalence of electronic cigarette use is increasing in children and adolescents.” (Page 8, lines 22-23). In fact, according to the latest statistics, e-cigarette use among young people in the United States fell this year by about one third compared to last year.

Ref:

FDA Press release. Results from 2018 National Youth Tobacco Survey show dramatic increase in e-cigarette use among youth over past year

Please see Table 1, answer 8.

664 Olteanu
Vlad, Juul
Labs Inc.,
Belgium

SUMMARY

Lines 9 to 20 of the Opinion summarize the main purpose of SCHEER’s review: “The Opinion addresses the role of electronic cigarettes, focussing into potential impacts on the EU context, in relation to: 1.their use and adverse health effects (i.e.; short-and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits) 2.their role as a gateway to smoking / the initiation of smoking (particularly focusing on young people) 3.their role in cessation of traditional tobacco smoking”. With respect to points 1 and 2 our response details a fundamental

Please see Table 1, answer 1.

critique of SCHEER's approach under our individual submissions registered under section 6 of the Opinion. On point 3, the SCHEER opinion dismisses the fact that electronic cigarettes are primarily used as alternatives to smoking (as indicated in the Eurobarometer reviews cited under the relevant points in our response) and that when used as a substitute for cigarettes, significantly reduce exposure to the harmful toxicants found in tobacco smoke. 26% of EU citizens are smokers. These smokers are at serious risk of disease and premature death—with 700,000 of them dying each year. This is the population most at risk of avoidable cancer and therefore the population that would most benefit from an effective EU Beating Cancer Plan. With this essential policy objective in mind, the risk of e-cigarette use must be positioned relative to the well-established risks of continuing smoking. The fundamental information about comparative risk is absent throughout SCHEER's Opinion, yet it is the central public health proposition that e-cigarettes can and do offer. Studies such as Stephens et al, 2018 or George et al, 2019 found, respectively, that e-cigarette users were typically exposed to 0.4% of the lifetime cancer risk of smokers and that evidence of significant improvements in cardiovascular outcomes in smoking switching to e-cigarettes do exist and are well proven. Such studies need to be thoroughly and fully reviewed by SCHEER in its Opinion. More fundamentally, SCHEER's assessment decides upon the strength of evidence of various risks registered throughout the Opinion. The strength of evidence under GRADE standards must be correctly applied. Strength of evidence should be not confounded with event incidence (likelihood of a consumer experiencing a positive or negative event) or the severity of the risk incurred (to what extent is that risk harmful to the user). It would, in theory, be possible to have strong evidence of a rare occurrence of a minor irritation to the respiratory system, for example, or even of a device explosion. But because the assessment provides no meaningful quantification and quantification of risk, it presents little value to policymakers. How often does a serious event occur? How can it be best prevented? Pragmatic and well documented, science-based answers to this question are much more relevant and useful to policymakers. Regrettably, SCHEER's Opinion provides no valid frame of reference for

The SCHEER sufficiently underpins the conclusions in the Opinion.

assessing the seriousness of the risks it discusses. Quoted studies were uploaded with this submission in full (as .pdf) or as a first page .jpg file –for reference purposes- where a full upload was not possible because of the 1MB file size upload limitation or because of copyright rules.

Ref:

McNeill (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020. A report commissioned by Public Health England

Stephens, W.E. (2017). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tobacco Control, 2017

George J et al. (2019) Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes Journal of the American College of Cardiology:26855 doi:10.1016/j.jacc.2019.09.067

665 Michel Nicolas,Asociation Romande des Professionnels de la Vape,Switzerland

SUMMARY

Page 8
 13 It is also interesting
 14 to note that a modified version of a popular pod device with a
 76% US-market share
 15 is now on the EU market, with technological adjustments.
 These figures are wrong. They come from Nielsen Data, which
 analyzed only the “tobacco channel”. This measure is not adequate
 for the vaping market because specialized shops order either
 directly from the manufacturer, or via specific vape wholesalers.
 In the USA, there are an estimated 15,000 companies specializing
 in vaping. They go under the Nielsen data radar. This shows that
 independent vaping players are being ignored in an effort to
 associate vaping with tobacco products and producers. In a more
 recent publication, Wells Fargo indicates that Juul has a 36.5%
 market share.

This has been replaced throughout the report by a ‘large market share’.

http://www.natocentral.org/uploads/Wall_Street_Update_Slide_Deck_February_2019.pdf

Page 29
 Estimating market share in an unstructured market is difficult, so
 these figures are very unreliable. In addition, Nielsen Data are
 intended for investors, so they are probably not interested in
 Chinese brands like Innokin, Aspire, Joyetech or GeekVape which,
 although they are dominant in the market, are not open to investors.
 Surprisingly, SMOORE is publicly traded and does not appear in
 these analyses, despite its market value being higher than Juul. This

is probably due to the fact that the products of the SMOORE group, such as Vapresso, are not distributed via the "tobacco channel".

Many studies, some of which you use, cite Nielsen data and say that Juul has 76% of the US market. This shows the incompetence of the authors and this is worrying for the quality of the research.

Page 91
37 Walley, S. C., Wilson, K. M., Winickoff, J. P., & Groner, J. (2019). A Public Health Crisis: 38 Electronic Cigarettes, Vape, and JUUL. Pediatrics, 143(6). doi:10.1542/peds.2018-2741

Most major e-cigarette brands are owned by big tobacco companies that use similar marketing and advertising strategies to attract youth users as they did with traditional tobacco products. In this review, we provide an overview of e-cigarettes and vape devices with an emphasis on the impact for the pediatric population. We describe the vast array of e-cigarette devices and solutions, concern for nicotine addiction, and the scientific background on the known health harms.

If the authors of this paper have such a misunderstanding of vape that they imagine that "BigT" owns the majority of the brands of vape, how can the rest of their work be credited? Yet this article is quoted in this report. This shows that the SCHEER expert group should have included a fields person.

666 Compernole
Thomas, British
American
Tobacco, Belgium

SUMMARY

The summary could benefit from inclusion of references to support key statements using only published findings (P6, LN25) or links to the main body of text. Where data has been considered, the report relies heavily on US data (P7, LN11-12 and P7, LN12-13) without mention of TPD2. The US e-cigarette market, consumer attitudes and legislation are significantly different to that of the EU and therefore more EU-centric data should be considered.

Please see Table 1, answers 1 and 8.

E-cigarettes have lower emissions and toxicants compared to cigarettes, but harm reduction initiatives (1,2,3) are not addressed. Regulatory accepted in vitro techniques (4,5,6,7,8) exist and are routinely employed and should be used in the weight of evidence

approach, rather than discounted in their entirety. Health effects focus predominately on CVD despite behavioral, environmental and genetic factors playing a significant role in other disease etiologies such as pulmonary disease (9,10). Moreover, CVD disease mechanisms in response to smoke are not well defined (11).

Divergence of e-cigarette technology is not considered, and all e-cigarettes format are considered equal in their risk. Misuse has a significant bearing on risk potential and again, is not considered (P13, LN12). New e-cigarette technologies (12) that could significantly impact absolute risk are not discussed.



C1R0_-_Section_1.0_
Summary_Reference_

667 Vuerich
Michela,A
NEC,
European
consumer
voice in
standardisa
tion,
Belgium

SUMMARY

Page 7, lines 5-11: The preliminary opinion is disappointing with respect to risk assessments of (individual) substances other than nicotine. We would have thought that this aspect should be in the centre of a scientific opinion addressing risks relating to vaping. In the summary this issue is dealt with in a mere 6 lines and also in the body of the opinion this topic is clearly underdeveloped (i.e. chapter 6.5). We understand, of course, that in an opinion like this it is impossible to conduct risk assessments for numerous substances. However, at least for some of them – particularly for those which have already been subject to more detailed assessments, debate and even normative provisions - SCHEER should demonstrate exemplarily how priority substances could be determined and how risk assessments could be performed for them and for which aspects further research is required. The statement that "there is no harmonised classification to clearly identify their hazards" may be correct but is not very relevant – many risk assessments are or have been performed for substances which do not have a harmonised classification. Apart from that also self-classifications by industry are relevant to determine relevant hazards.

At the end of the day the question is which further activities should be initiated and how the risks associated with the inhalation of chemicals can be minimised. Otherwise we run the risk is that no

Please see Table 1, answer 3.

action will follow. We strongly believe that this should be avoided and policy makers should get clear recommendations rather than getting the message that there is much uncertainty and little can be done regarding most substances lacking toxicological data. Further comments are provided in the relevant sections.

Page 8, lines 28-29: The text before the lines concluding "that there is strong evidence that electronic cigarettes are a gateway to smoking for young people" addresses the attractiveness of flavours but does not provide any arguments for the conclusion. If flavours are so attractive why should adolescents then switch to non-flavoured conventional cigarettes? And why is the prevalence of smoking decreasing when increased use of e-cigarettes is a "gateway" to smoking? The gateway theory is controversial – but SCHEER does not explain why it supports it despite opposing studies. More comments are provided in the relevant section.

Page 8, lines 48-49: The text before provides some data indicating that more people tried to get rid of smoking by using e-cigarettes but no data concerning the success of these efforts. Even if the studies are not necessarily reliable it would nevertheless be useful to give the reader an idea about reported data.

668 Lippmann Christian, Interessengemeinschaft E-Dampfen e.V., Germany

SUMMARY

Interessengemeinschaft E-Dampfen e.V. (IG-ED) is the German consumer association for vapers, independent of the industry. We see in e-cigarettes a strong alternative for smokers who are not able to quit smoking. It also is a strong tool in minimizing the Non-Communicable Diseases. See our statement: IG-ED Statement: [Attachment: 01_Statement_of_IG-ED_on_WHO-Consultation_on_Non-Communicable Diseases_-_Interessengemeinschaft_E-Dampfen_e.V_.pdf] Ref: Statement of IG-ED on WHO Consultation on Non-Communicable Diseases

Please see Table 1, answer 1.



01_Statement_of_IG-ED_on_WHO-Consultation

669 Lippmann Christian, I

SUMMARY

Page 6 Line 47-53 In general, e-cigarettes have been on the market for nearly 10 years.

Please see Table 1, answer 1.

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Millions of people worldwide were able to stop the harmful smoking when they have switched to vaping. The overwhelming scientific consensus is that vaping is much less harmful than smoking. It's on the level of caffeine or NRT.

Study: Nicotine “no more harmful to health than caffeine”
[Attachment: 02_RSPH _ Nicotine_“no more harmful to health than caffeine”.pdf]

Study: Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study
[Attachment: 03_Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users_ A Cross-sectional Study_ Annals of Internal Medicine_ Vol 166, No 6.pdf]

See Table 1, answer 9.

The nicotine in liquids is variable. According to TPD2 in the EU only the range of 0 mg/ml up to 20 mg/ml is allowed to be sold. This limit is already very arbitrary because the evidence shows that also higher level of nicotine provide no issues to the consumer.

Especially the variability of the nicotine in liquids help smokers to find their level for a successful switch from smoking to vaping. Most of the people start with a higher level of nicotine and after successfully switching, they reduce it automatically (self titration).

Nicotine is not the main health problem, it is the combustion of cigarettes which can cause illness. There are no studies that show any nicotine dependence on nicotine patches, gums or inhalers from the pharmacy.

The LD50 of nicotine according to literature is often not correct and outdated.

Study: How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century
[Attachment: 04_How much nicotine kills a human_ Tracing back

the generally accepted lethal dose to dubious self-experiments in the nineteenth century – SpringerLink.pdf]

There are only rare cases available, where users get an overdose of nicotine liquid. Most of them get well soon. To avoid this in the EU liquids are sold with childproof locks.

Furthermore, explosions -- correct: venting batteries -- are very rare. Most of the affected users did not observe basic battery safety guides. This can happen with each technical products using batteries.

Ref:

RSPH (2015). Nicotine no more harmful to health than caffeine. Press release. <https://www.rsph.org.uk/about-us/news/nicotine--no-more-harmful-to-health-than-caffeine-.html>

Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. (2017). Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. *Ann Intern Med.* 2017 Mar 21;166(6):390-400. doi: 10.7326/M16-1107

Mayer B. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch Toxicol.* 2014;88(1):57. doi:10.1007/s00204-013-1127-0

670 Lippmann Christian, Interessengemeinschaft E-Dampfen e.V. (IG-ED), Germany

SUMMARY

PAGE 7 Line 28-42
There is no strong evidence that young people are using e-cigarettes permanently. Several studies show that many try it just out of curiosity. Most of them are adolescents already experimenting with smoking. The level of curiosity seems strongly correlated to the prevalence of educational material targeting juveniles. There is absolutely no actual survey data supporting a hypothetical gateway from vaping to smoking. E-Cigarettes are a gateway out of smoking.

Please see Table 1, answer 5.

Study: Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? [Attachment: 05_Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France_ - ScienceDirect.pdf]

Study: Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey [Attachment: 06_Youth Vaping and Tobacco Use in Context in the

United States_ Results From the 2018 National Youth Tobacco Survey _ Nicotine & Tobacco Research _ Oxford Academic.pdf]

Study:Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study [Attachment: 07_Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents_ a cross-sectional, matched control study _ Tobacco Control.pdf]

Ref:

Chyderiotis S, Benmarhnia T, Beck F, Spilka S, Legleye S (2020) Does e-cigarette experimentation increase the transition to daily smoking among young ever-smokers in France? Drug and alcohol dependence 208:107853 doi:https://doi.org/10.1016/j.drugaledep.2020.107853

Glasser AM, Johnson AL, Niaura RS, Abrams DB, Pearson JL (2020) Youth Vaping and Tobacco Use in Context in the United States: Results from the 2018 National Youth Tobacco Survey Nicotine & Tobacco Research doi:10.1093/ntr/ntaa010

Shahab L, Beard E, Brown J (2020) Association of initial e-cigarette and other tobacco product use with subsequent cigarette smoking in adolescents: a cross-sectional, matched control study Tobacco control:tobaccocontrol-2019-055283 doi:10.1136/tobaccocontrol-2019-055283;

https://www.eurekalert.org/pub_releases/2020-03/b-oe031320.php

671 Lippmann Christian, I
nteressengemeinschaft E-Dampfen e.V. (IG-ED), Germany

SUMMARY

PAGE 7 Line 44-57

Flavours in the e-liquids are the key element for success. Adult smokers who like to quit smoking are able to switch to e-cigarettes as there are many flavours available. They don't like any tobacco flavours anymore. Reducing the availability of flavours to tobacco and menthol only, will lead to less vapers but more smokers.

Please see Table 1, answer 5 and 7.

Study:Should flavours be banned in cigarettes and e-cigarettes? Evidence on adult smokers and recent quitters from a discrete choice experiment

[Attachment: 08_Should flavours be banned in cigarettes and e-cigarettes_ Evidence on adult smokers and recent quitters from a discrete choice experiment _ Tobacco Control.pdf]

Flavours in liquids are also very important for the smokers to switch completely to vaping and prevent the vapers to switch back to smoking.

Study:

Longitudinal Analysis of Associations Between Reasons for

			Electronic Cigarette Use and Change in Smoking Status Among Adults in the Population Assessment of Tobacco and Health Study [Attachment: 09_Longitudinal Analysis of Associations Between Reasons for Electronic Cigarette Use and Change in Smoking Status Among Adults in the Population Assessment of Tobacco and Health Study _ Nicotine & Tobacco Research _ Oxford Academic.pdf]	
672	Lippmann Christian, Interessengemeinschaft E-Dampfen e.V. (IG-ED), Germany	SUMMARY	<p>PAGE 8 Line 8-20</p> <p>Nicotine is a very important key element in liquids for smokers to be able to quit smoking with the help of e-cigarettes. Nicotine itself is not carcinogenic, it is the smoke and the tar of tobacco cigarettes. Study:IARC: Does nicotine cause cancer? [Attachment: 10_European Code Against Cancer - Does nicotine cause cancer_.pdf]</p> <p>In the EU the arbitrarily set limit of 20 mg/ml maximum nicotine concentration. The US-Product JUUL had to react on this and lower down the nicotine salt pods of their product. This didn't work in the EU and so JUUL announced to leave the European market, especially from Germany.</p> <p>News Platform E-Zigarettenhersteller Juul zieht sich aus Deutschland zurück [Attachment: 11_E-Zigarettenhersteller_ Juul verschwindet in Deutschland.pdf]</p> <p>Ref: European Code Against Cancer - Does nicotine cause cancer? https://cancer-code-europe.iarc.fr/index.php/en/ecac-12-ways/tobacco/199-nicotine-cause-cancer</p> <p>E-Zigarettenhersteller Juul zieht sich aus Deutschland zurück. https://www.wiwo.de/unternehmen/handel/verdampfer-e-zigarettenhersteller-juul-zieht-sich-aus-deutschland-zurueck/26278674.html</p>	See table 1, answer 9.
673	Lippmann Christian, Interessengemeinschaft E-Dampfen e.V. (IG-	SUMMARY	<p>PAGE 8 Line 34- 53</p> <p>The evidence is very strong, that smokers trying e-cigarettes are more likely to quit smoking compared to trying abstinence or NRTs (nicotine replacement therapy). Study:A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy [Attachment: 12_A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy _ NEJM.pdf]</p>	Please see Table 1, answers 1, 5 and 6.

	<p>ED),Germany</p> <p>The success rate of quitting with E-Cigarettes is much higher with nicotine liquids than with nicotine free liquids. Study:E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. [Attachment: 13_E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run_ Preliminary Results by Randomized Controlled Trial _ Nicotine & Tobacco Research _ Oxford Academic.pdf]</p> <p>At least the cost-effectiveness supporting e-cigarettes is better than prescribed NRTs. Study:Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial [Attachment: 14_Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study)_ a randomized controlled trial - Li - 2020 - Addiction - Wiley Online Library.pdf]</p> <p>In summary, IG-ED recommends e-cigarettes as an effective tool for tobacco harm reduction. The evidence shows that e-cigarettes support a rapid decline in smoking. Additional regulations on top of TPD2 will lead to the result that less smokers switch to the much more harmless alternative. Also it should be well known, that more strict regulations will lead to harmful black market activities of the consumers. If the health of the people really matters, the EU should support e-cigarettes as an alternative for smokers.</p> <p>Ref: Hajek (2019) A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. DOI: 10.1056/NEJMoa1808779 Li (2019). Cost-effectiveness of e-cigarettes compared with nicotine replacement therapy in stop smoking services in England (TEC study): a randomized controlled trial. https://doi.org/10.1111/add.14829 Masiero (2020). E-cigarettes May Support Smokers With High Smoking-Related Risk Awareness to Stop Smoking in the Short Run: Preliminary Results by Randomized Controlled Trial. https://doi.org/10.1093/ntr/nty047</p>	
<p>674 Vuerich Michela,A NEC, European Consumer voice in</p>	<p>SUMMARY</p> <p>Page 7, lines 5-11: The preliminary opinion is disappointing with respect to risk assessments of (individual) substances other than nicotine. We would have thought that this aspect should be in the centre of a scientific opinion addressing risks relating to vaping. In the summary this issue is dealt with in a mere 6 lines and also in the body of the opinion this topic is clearly underdeveloped (i.e. chapter</p>	<p>Please see Table 1, answers 1 and 3.</p>

standardisation, Belgium

6.5). We understand, of course, that in an opinion like this it is impossible to conduct risk assessments for numerous substances. However, at least for some of them – particularly for those which have already been subject to more detailed assessments, debate and even normative provisions - SCHEER should demonstrate exemplarily how priority substances could be determined and how risk assessments could be performed for them and for which aspects further research is required.

The statement that "there is no harmonised classification to clearly identify their hazards" may be correct but is not very relevant – many risk assessments are or have been performed for substances which do not have a harmonised classification. Apart from that also self-classifications by industry are relevant to determine relevant hazards.

At the end of the day the question is which further activities should be initiated and how the risks associated with the inhalation of chemicals can be minimised. Otherwise we run the risk is that no action will follow. We strongly believe that this should be avoided and policy makers should get clear recommendations rather than getting the message that there is much uncertainty and little can be done regarding most substances lacking toxicological data. Further comments are provided in the relevant sections. Page 8, lines 28-29: The text before the lines concluding "that there is strong evidence that electronic cigarettes are a gateway to smoking for young people" addresses the attractiveness of flavours but does not provide any arguments for the conclusion. If flavours are so attractive why should adolescents then switch to non-flavoured conventional cigarettes? And why is the prevalence of smoking decreasing when increased use of e-cigarettes is a "gateway" to smoking? The gateway theory is controversial – but SCHEER does not explain why it supports it despite opposing studies. More comments are provided in the relevant section.

See the answer to the specific chapter.

Page 8, lines 48-49: The text before provides some data indicating that more people tried to get rid of smoking by using e-cigarettes but no data concerning the success of these efforts. Even if the

studies are not necessarily reliable it would nevertheless be useful to give the reader an idea about reported data.

675	Clark Alex, The Consumer Advocates for Smoke-free Alternatives Association (CASAA), United States	SUMMARY	<p>Pg. 8 - Line 14</p> <p>Throughout the SCHEER report, a “popular pod device with a 76% US-market share” is referenced. The SCHEER statement lacks context. The penultimate source referenced by Fadus, et al contextualizes this number by noting that JUUL’s market share is only measured as a percentage of Neilson-tracked retail channels. There remains a large segment of the vapor industry that is not tracked by Neilson and is estimated to make up 30% to >50% of the overall nicotine vapor market. "E-cig category dollar sales were \$408.5MM this period implying about ~\$4.6B annual retail sales in Nielsen-tracked channels (vs \$3.3B in 2018). Considering Nielsen underestimates and doesn’t capture all of the channels where e-cigs/vapor products are sold such as online, vape shops, etc, we estimate the total category will reach approximately \$9.0B by the end of 2019 (vs ~\$7.0B in 2018)." (Herzog 2019)</p> <p>Herzog, Bonnie, and Patty Kanada. Wells Fargo, 2019, pp. 11, Nielsen: Tobacco All Channel Data Thru 9/7 - Cig Vol Declines Hold Steady.</p>	<p>This has been replaced throughout the report by a ‘large market share’.</p> <p>Thank you for the comment: The text of the Opinion was amended</p> <p>See also the answer to question 15</p>
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676	Woessner Julie, International Network of Nicotine Consumer Organizations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU	SUMMARY	<p>The Summary section summarizes many of the issues explored in more depth in the body of the Preliminary Opinion. We have provided substantive comments on those sections, but note here that this section is one of the three sections (Abstract, Summary, Scientific Opinion) that many, if not most, people will rely upon to gain an understanding of SCHEER’s findings. Therefore, the selection of the information to be contained in this section is crucial to avoid misleading or misinforming readers.</p> <p>Page 6 / lines 24 - 25</p> <p>For purposes of transparency, which organisations reported and how? What information did the Commission provide?</p> <p>Page 7 / Line 14</p> <p>SCHEER neglected to report in the Summary its risk assessments as found at page 13, line 34; and page 54, line 48 (“Therefore, the related risk is low.”); and at page 62 line 8 (“Therefore, the risk is expected to be low.”).</p>	<p>See the answers to the specific chapters.</p>
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Page 7 / lines 32-33 and 46-47
See our comments on Section 6.6 regarding the confusion caused by failure to identify age ranges.

Page 7 / Lines 38-42
SCHEER presents no evidence that trends in the US are influencing the EU market, and so we question the value of the use of so much US data. This is especially true given the significant differences in these two markets given the protections afforded in the EU by the TPD versus the US market with no standards-based regulation.

Page 7 / Line 52-55
See our comments on Section 6.6 regarding the confusion caused by failure to identify age ranges.

Page 8 / Lines 13-20
We question as to why a single product, that is clearly not representative of the EU market, is a focus by SCHEER in the Summary?

Page 8 / Lines 22-32
See our comment on the gateway hypothesis in the TERMINOLOGY section. US “trends” centric, only “some data from the US” ends up in strong evidence opinion on the gateway hypothesis. The SCHEER carefully avoided to compare vaping to smoking through all its Opinion. Even when trying to assess the gateway hypothesis it fails to take into account the smoking prevalence. A simple rise in use of vaping devices is not enough to assess the gateway hypothesis. We submit that SCHEER should clearly define the term ‘gateway’ and adopt standard verification models to assess this hypothesis within an EU context. For example: In the context of this assessment, the gateway hypothesis is adapted to denote the use of less harmful forms of nicotine delivery (e.g., e-cigarettes), leading to the use of more harmful ones (e.g., combustible cigarettes). It should be noted that the term is generally conjoined with ‘hypothesis’, denoting the absence of widespread evidence of its occurrence.

677 Farsalinos SUMMARY
Konstantin

Page 6, line 2 to page 8, line 53
The primary reasons for the failure of the Scheer report to provide

For comparison with smoking: see Table 1, answer 1.

os,Universi
ty of
Patras,
Greece

an evidence-based scientific opinion with would be useful for
policy makers and the public are:

1. No consideration that the vast majority of e-cigarette users are current or former smokers. Strong health benefits are expected in smokers who have managed to quit smoking with the help of e-cigarettes, while benefits may be expected even for dual users if they have substantially reduced their smoking consumption. As a result, the report is misinformative and potentially misleading.
2. No comparison with the well-established harmful effects of tobacco cigarette use. This is directly related to the previous point about the smoking status of e-cigarette users.
3. Poor quantitative definition of exposure risk. The report seems to consider mostly the presence of chemicals without adequately quantifying the pragmatic risk using established comparators, such as occupational exposure or even environmental safety limits. Furthermore, problems in the understanding of use patterns and consumption measures were noted, with the emissions of several compounds being reported as amount per puff while the true measure of consumption is volume (or weight) of liquid per day.
4. Misinterpretation studies on e-cigarette and tobacco use among youth as indicative of a gateway-to-smoking effect. The report fails to consider the common liability model, which is much more applicable in explaining the risk-prone behavior of youth who engage to e-cigarette use, smoking and use of other substances such as marijuana and alcohol.
5. Unrealistic concerns about the lack of long-term studies. It is unrealistic to expect product-specific long-term epidemiological-population studies. The large variability of different devices and liquids is a necessity to satisfy different needs to adult smokers. Thus, e-cigarettes should be treated as a group of products when examining health effects rather than expecting product-specific data.
6. Failure to differentiate acute from chronic effects of e-cigarette use on the cardiovascular system and misinterpreting findings on acute effects as indicative of long-term harm. Markers of cardiovascular health, mainly measurements of vascular function, have no prognostic value when measured during an acute intervention. Instead, data have shown substantial benefits for

For the methodology applied: See Table 1, answer 3. The SCHEERs does not consider consumption of liquid per day an appropriate basis for the exposure and risk assessment.

The SCHEER does not ignore variability and does not ask for “product-specific” long-term data.

smokers who switch to e-cigarette use when these markers are measured at resting conditions according to established guidelines. As a result, the Scheer report concluded that the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong, which is contradicting the available evidence of cardiovascular benefits for smokers who switch to e-cigarettes.

7. Use of outdated, non-clinical evidence about cardiovascular risks of nicotine, while long term epidemiological studies of snus use has shown minimal adverse effects of sustained nicotine intake through a non-combustible source.

8. Presentation and use of other opinion pieces and conclusions (Surgeon General Report, European Heart Network report). It appears that these reports have been used as arguments for the recommendations and conclusions of the Scheer report. This raises the issue of bias and defies the purpose of the report which was expected to be an independent systematic review of the available evidence.

678 Pooler Marc,UK Vaping Industry Association,United Kingdom

SUMMARY

The UKVIA supports the UK's vapers, with around 3.2 million (1) in Great Britain alone . Across the UK there are around 7 million smokers (2) who are yet to quit or switch to a less harmful alternative. Indeed, statistics show that over half of smokers in Great Britain want to quit. (3) In this context we are supportive of evidence-based regulation which notes that, while not risk-free, vaping is a less harmful alternative for adults who would otherwise continue to smoke. We believe it is important to acknowledge the public health benefits that vaping products may have on reducing smoking prevalence overall.

- The SCHEER opinion dismisses the fact that electronic cigarettes are primarily used as alternatives to smoking.
- A fundamental acknowledgement of the difference in comparative risk between e-cigarettes and combustible cigarettes is entirely absent in this opinion. In particular, that e-cigarettes are a less harmful alternative to smoking, Public Health England have said that best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether (4).
- The European Commission's own figures state that 26% of EU citizens smoke and that they are at the most serious risk of disease

For comparison with smoking: see Table 1, answer 1.

and premature death – with 700,000 of them dying each year (5).

- If the Commission is serious about reducing smoking prevalence across Europe, then acknowledging the positive public health role that vaping products could play in a healthier Europe is fundamental to making that plan a success.
- The Royal College of Physicians stated in 2019 that ‘E-cigarettes are effective in helping people to stop smoking’ (6) and Cancer Research UK have said, ‘There is growing evidence that e-cigarettes are an effective quitting tool’. (7)

- (1) Action on Smoking and Health, 2020
 (2) Office National Statistics, 2020
 (3) Office National Statistics, 2020
 (4) Public Health England, 2015
 (file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Public%20Health%20England%202015.pdf)
 (5) European Commission, 2020 (https://ec.europa.eu/health/tobacco/overview_en)
 (6) Royal College of Physicians, 2019
 (file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Royal%20College%20of%20Physicians%202016.pdf)
 (7) Cancer Research UK, 2018
 (file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Cancer%20Research%20UK%202018.pdf)

679 Moiroud Jean, Fédération Interprofessionnelle de la Vape (FIVAPE), France

SUMMARY

FIVAPE welcomes the high quality of synthesis of the SCHEER’s work on this preliminary opinion. However, we deem it necessary to add several comments on some of the elements brought forward in this opinion.

Regarding the role of vaping products in cessation of traditional tobacco smoking (p. 8, point 3, lines 34-53):

- We regret that the report does not analyse the effects of vaping products in comparison to those of cigarettes, which are scientifically proven to be harmful.
- It should be clearly reminded that the goal is to offer harm reduction solutions in order to help smokers quit. These solutions, such as vaping, are aligned with the objectives of the EU’s Beating Cancer Plan, expected to be published at the end of the year.
- What is tobacco harm reduction? European Tobacco Harm Reduction Advocates (ETHRA) defines tobacco harm reduction as “a range of public health and other evidence-based policies, designed to lessen the negative social and/or physical consequences associated with smoking. It endorses the use of novel nicotine

For comparison with smoking: see Table 1, answer 1.

products and supports research into their safety and efficacy. Tobacco harm reduction is a consumer led approach which enables smokers and ex- smokers to make informed choices regarding safer nicotine products.”

- Tobacco has clearly been identified throughout the years as the leading cause of preventable deaths in the EU and the leading cause of preventable cancers. Harm reduction solutions such as vaping, which aim to address tobacco and its deadly consequences, should be put forward and prioritize in order to achieve the Cancer Plan’s main objectives.

Here are some articles that need to be consider on this chapter:

- On cancer risks: “Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke”, Stephens et al, 2018. Link : <https://tobaccocontrol.bmj.com/content/27/1/10>

- On cardiovascular risks: “Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes”, George et al, 2019. Link : <https://www.onlinejacc.org/content/74/25/3112>

We would like to thank the SCHEER for giving stakeholders the occasion to provide feedback on this crucial preliminary report.

Ref:

Stephens WE (2018). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. <https://tobaccocontrol.bmj.com/content/27/1/10>

George et al. (2019). Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. <https://www.onlinejacc.org/content/74/25/3112>

680 Pooler SUMMARY

Marc,UK
Vaping
Industry
Associatio
n,United
Kingdom

Conclusion
We therefore call upon the Commission to recognise the role that e-cigarettes can play in providing adult smokers with a less harmful alternative to cigarette smoking. We urge the Commission to ensure that the public health potential of vaping is fully realised, and that adult smokers and vapers have accurate information about and access to the harm reduction products they need.

For comparison with smoking: see Table 1, answer 1.

681 't Hart SUMMARY

Emil,Elekt
ronische
Sigaretten
Bond
Nederland,

SCHEER ignores the harm reduction benefits of e-cigarettes for individual adult smokers who switch to e-cigarettes as well as for the society as a whole. Responsible national anti-smoking policies should therefore provide fact-based information on e-cigarettes and encourage smokers to fully switch to e-cigarettes.

For comparison with smoking: see Table 1, answer 1.

682 Pooler Marc,UK Vaping Industry Association,United Kingdom SUMMARY The UKVIA supports the UK’s vapers, with around 3.2 million in Great Britain alone (1). Across the UK there are around 7 million smokers (2) who are yet to quit or switch to a less harmful alternative. Indeed, statistics show that over half of smokers in Great Britain want to quit. (3) For comparison with smoking: see Table 1, answer 1.

In this context we are supportive of evidence-based regulation which notes that, while not risk-free, vaping is a less harmful alternative for adults who would otherwise continue to smoke. We believe it is important to acknowledge the public health benefits that vaping products may have on reducing smoking prevalence overall.

- The SCHEER opinion dismisses the fact that electronic cigarettes are primarily used as alternatives to smoking.
- A fundamental acknowledgement of the difference in comparative risk between e-cigarettes and combustible cigarettes is entirely absent in this opinion. In particular, that e-cigarettes are a less harmful alternative to smoking, Public Health England have said that best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether (4).
- The European Commission’s own figures state that 26% of EU citizens smoke and that they are at the most serious risk of disease and premature death – with 700,000 of them dying each year (5).
- If the Commission is serious about reducing smoking prevalence across Europe, then acknowledging the positive public health role that vaping products could play in a healthier Europe is fundamental to making that plan a success.
- The Royal College of Physicians stated in 2019 that ‘E-cigarettes are effective in helping people to stop smoking’ (6) and Cancer Research UK have said, ‘There is growing evidence that e-cigarettes are an effective quitting tool’. (7)

(1) Action on Smoking and Health, 2020
 (2) Office National Statistics, 2020
 (3) Office National Statistics, 2020
 (4) Public Health England, 2015

(https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/733022/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf)

(5) European Commission, 2020 (https://ec.europa.eu/health/tobacco/overview_en)

(6) Royal College of Physicians, 2016 (<file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Royal%20College%20of%20Physicians%202016.pdf>)

(7) Cancer Research UK, 2018 (<file:///C:/Users/user/Documents/JBP/UKVIA/SCHEER%20Documents/Cancer%20Research%20UK%202018.pdf>)

683	Schmidt Norbert, Intereisenmeinschaft E-Dampfen e.V. (IG-ED), Germany	SUMMARY	<p>P 8 L 28-29</p> <p>Quotes from the uploaded study: (CONSTANCES cohort, 2014) "Trends over one year show that no E-cig exclusive user had become a smoker one year later." "These preliminary findings do not show that the use of E-Cig induces initiation to smoking, and suggest it is rather largely used for trying to quit tobacco-smoking." Ref: Goldberg (2014). Utilisation de la cigarette électronique et du tabac : premières données de la cohorte Constances, France, 2014 // Electronic cigarette and tobacco smoking: preliminary results from the CONSTANCES cohort, France</p>	Please see Table 1, answer 1.
684	Kuttruf Andrej, Eva, United Kingdom	SUMMARY	<p>Same as the abstract the Summary follows the same loose use of terms such as 'weak' or 'strong', which are basically meaningless as they don't manage to quantify or provide context for this label.</p> <p>Points worth making: Summary, Nr.1 'the nicotine intake from e-cigarettes can be comparable to combustible tobacco' - this should actually be the objective. As the saying goes, 'smokers smoke for the nicotine, but die from the tar' - it is the combustion of tobacco in smoking, which causes most of the health risks and cancer causing carcinogens. If there is a substitute product, which delivers the nicotine in a far less harmful way, and finds wide adoption among smokers, this will lead to harm reduction.</p> <p>The note, that there is 'moderate ... level of evidence that e-cigarettes use has harmful effects' is misleading at best. Royal College of Physicians has evidenced that 'the hazard to health arising from long-term vapour inhalation from the e-cigarettes</p>	The SCHEER refers to the Guidance on the weight of evidence for clarification of these terms (SCHEER 2018, Memorandum on weight of evidence and uncertainties).

available today is unlikely to exceed 5% of the harm from smoking tobacco.' <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction>

The comparison should be the evidence of harm caused by cigarettes, which causes 700 000 deaths every year in Europe.

Summary, Nr.2: There is no reason why the document largely relies on data drawn from the US. There is enough data and studies available in the EU, which has a huge vaping population. The US market had no regulation, and the purpose of the document should be to evaluate the TPD regulation, which is in place in Europe since 2017.

It is worth noting that the document mentions that use of flavours carries no extra health risk in e-liquids but the debate of the role of flavours seems to be going into the wrong direction. Flavours make e-cigarettes more attractive to smokers and as such entice smokers to switch away to a far less harmful alternative.

'If [a risk-averse and precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.' <https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction> (Section 12.10 page 187)

There is no evidence that flavours lead to uptake of youth vaping as evidenced by the low uptake of vaping among the youth. <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#the-use-of-electronic-cigarettes-e-cigarettes-great-britain>

There is no gateway effect to smoking. 'Only 0.8% of people who have never smoked reported that they currently vape.' <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#the-use-of-electronic-cigarettes-e-cigarettes-great-britain>

ndsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#the-use-of-electronic-cigarettes-e-cigarettes-great-britain

Summary, Nr 3:
Plenty of studies show the effect of e-cigarettes in helping smokers to quit smoking: 'E-cigarettes were more effective for smoking cessation than nicotine-replacement therapy' Hajek et al 2019, <https://www.nejm.org/doi/full/10.1056/NEJMoa1808779>

As well as evidenced by the steep decline of smoking rates in markets, where vaping has been adopted more widely: (UK, <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2018#the-use-of-electronic-cigarettes-e-cigarettes-great-britain>)

Terms of Reference:
As pointed out above, the reference for a holistic policy review of TPD should be the comparison with the harm caused by smoking.

685	Poirson Philippe, Sovape, France	TERMINOLOGY	[p. 19 l. 54-55] The term “electronic cigarette” is not neutral as it links to cigarette and to the old world tobacco paradigm. The “preference” of the SCHEER show an a priori ideological position, not a scientific consideration.	The SCHEER used the terminology and definition from the TPD: ‘electronic cigarette’ means a product that can be used for consumption of nicotine-containing vapour via a mouth piece, or any component of that product, including a cartridge, a tank and the device without cartridge or tank. Electronic cigarettes can be disposable or refillable by means of a refill container and a tank, or rechargeable with single use cartridges;
686	No agreement to disclose personal data	TERMINOLOGY	SCHEER does not use the term “vaping” as it may imply that the consumption of e-cigarettes is a “healthy” alternative to smoking and consumers may misperceive risks associated with the use of e-cigarettes. Vaping is clearly defined in the Oxford dictionary as “the action or practice of inhaling and exhaling vapour containing nicotine and flavouring produced by a device designed for this purpose” and is being fully defined in the EU CEN/TC 437/WG 1 “Terminology and definitions” product standardisation working group (PWI00437008). By avoiding the common definition and language used by consumers, regulators and public health bodies, it is unhelpful and confusing to readers. E-cigarettes do not contain or burn tobacco and therefore don’t produce smoke. It is therefore	Vaping has associations with vapour, suggesting harmless exposure. Since the ToR ask for an assessment of exposure to e-cigarette aerosol and second hand exposure per se, the SCHEER considers the term vaping inappropriate.

not possible to “smoke” an e-cigarette. This poor use of language conflates the action of smoking a combustible cigarette with the use of an e-cigarette, E.g.:

- Electronic cigarette smoking sessions instead of electronic cigarette vaping sessions (pg 14 line 16);
- Smokers protocols instead of vaping protocols (pg 26 line 49);
- Electronic cigarette smoking behavior instead of electronic cigarette vaping behavior (pg 26 line 53);
- Smoking device instead of vaping device (pg 32 line 4).

687 Compernelle
Thomas, British
American
Tobacco, Belgium

TERMINOLOGY

SCHEER applied a broad definition of e-cigarette use in its evidence synthesis that fails to take into account frequency of e-cigarette use or e-cigarette use patterns. Therefore, it is impossible to draw conclusions on a causal association between e-cigarette use and cigarette smoking initiation or cessation. Simply measuring “ever” or “current” use is inadequate—particularly in adolescents—as these measures are heterogeneous categories incorporating experimental, occasional, and regular use (1, 2).

SCHEER considers this comment out of scope. No changes needed.

The strongest evidence for evaluating cigarette smoking initiation is provided by studies of regular e-cigarette use transitioning to regular cigarette smoking. Conversely, the weakest evidence is provided by studies of use that are in line with e-cigarette and cigarette experimentation, which may or may not contribute to established product use behaviors.

Looking at the frequencies of e-cigarette use applied by studies included in a recently completed systematic review on the potential associations between e-cigarette use among nonusers of tobacco and initiation of cigarette smoking, no studies evaluated regular e-cigarette use transitioning to regular cigarette smoking. Furthermore, only one of 48 studies evaluated the association between regular e-cigarette use and any measure of cigarette smoking initiation—specifically, weekly/daily e-cigarette use to “ever having smoked a whole cigarette” (3).

The recent systematic review also stratified outcome measures by “initiation” (any cigarette use) and “initiation and progression to regular cigarette smoking” (daily, weekly, or current established cigarette use). Among the 44 initiation studies, “ever” use was the

most common measure for both e-cigarette use (36 studies) and cigarette use (34 studies); among the 10 studies evaluating cigarette smoking progression, “ever” e-cigarette use again was the most commonly applied definition of e-cigarette use (5 studies) (3). (The sum of e-cigarette use measures may not equal the overall number of studies due to the application of multiple measures in some studies).

Similarly, the strongest evidence for evaluating cigarette smoking cessation is provided by studies of regular e-cigarette use transitioning to sustained and prolonged smoking abstinence. Conversely, the weakest evidence is provided by studies of use that are in line with e-cigarette experimentation, which is unlikely to contribute to smoking cessation among regular cigarette smokers.

A second systematic review on associations between e-cigarette use among cigarette smokers and changes in continued smoking identified 101 studies evaluating cigarette use and abstinence/quitting cigarette smoking, of which 38 studies evaluated regular e-cigarette use (4). Current (any past 30-day) e-cigarette use was the definition used in 50 studies, while “ever” e-cigarette use was used in 23 studies. (The sum of e-cigarette use measures may not equal the overall number of studies due to the application of multiple measures in some studies).

Furthermore, the second systematic review identified 81 studies that examined e-cigarette use and change in cigarette smoking quantity/frequency (reduction), of which 38 studies evaluated regular e-cigarette use. Current e-cigarette use was the definition used in 38 studies, while “ever” e-cigarette use was used in 16 studies (4). (The sum of e-cigarette use measures may not equal the overall number of studies, due to the application of multiple measures in some studies).

In conclusion, the determination of causal associations between e-cigarette use and cigarette smoking initiation and cessation must be guided by the highest level of evidence, which would include measures of regular use for both e-cigarettes and cigarettes (1, 2).
Ref:

Etter JF. Gateway effects and electronic cigarettes. *Addiction*. 2018;113(10):1776-83.

Glasser A, Abudayyeh H, Cantrell J, Niaura R. Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. *Nicotine and Tobacco Research*. 2019;21(10):1320-30.

Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use among Non-Tobacco Users and Initiating Smoking of Combustible Cigarettes. 2019.

Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use Among Cigarette Smokers and Changes in Continued Cigarette Smoking. 2020.

Etter, J.F. (2018). Gateway effects and electronic cigarettes. *Addiction* 113: 1776-1783

Glasser (2018). Patterns of E-Cigarette Use Among Youth and Young Adults: Review of the Impact of E-Cigarettes on Cigarette Smoking.

688 Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association with 35 orgs all over the world and 15 from the EU

TERMINOLOGY

The terminology section of the SCHEER Opinion seems poorly populated considering the many concepts that are used but not well defined. More definitions would help to clarify the debates. We ask the SCHEER committee to clearly define the following concepts/words:

Nicotine

The SCHEER should clearly delineate between different kinds of nicotine using the appropriate terminology. There are differences between tobacco smoked nicotine with increased addictive properties due to tobacco additives (combustible nicotine) and non-smoked, high-purity nicotine as found in European vaping products, thanks to the TPD Art. 20.3(d) (high-purity nicotine). This differentiation is essential when discussing nicotine's addictiveness and its health impact. "Some 72-92% of adult cigarette smokers meet the criteria for dependence. While nicotine is recognised as an addictive substance in the tobacco leaf, the risk of addiction to pure nicotine products is very low compared to cigarettes." SCENIHR, Addictiveness and Attractiveness of Tobacco Additives, 2010 (cited by SCHEER)

Addiction/dependency

The SCHEER should clearly define what addiction and dependency are and the differences between the two related to a substance use. In the scope of this Opinion, related to high-purity nicotine use through vaping. At the very least, the SCHEER should inform on which previous addiction/dependency definitions this Opinion is based and how these definitions are met for high-purity nicotine use through vaping. It's the first step to correctly assess

The SCHEER based the Opinion on the information on the chemicals in the aerosol, independently from the nicotine grading.

The SCHEER based its Opinion on internationally accepted methodologies for risk assessment.

addiction/dependency risks.
 Gateway hypothesis
 The SCHEER should clearly define what is the gateway hypothesis for nicotine and how to test it in the real world. Through all the Opinion it should be clearly stated that it's only a hypothesis. "Clearly, as an account of human behavior, there is a degree of seductiveness to the idea that exposure to a single substance will lead people inexorably down a path of vice they would not otherwise have succumbed to (whether it be addiction, promiscuity, violence, and so on). For if the substance is the problem, the answer then becomes simple: limit exposure. Although the breadth of the gateway trope would suggest a dampening of the meaning of the concept, its potency nevertheless comes in part from its veneer of scientific credibility. This is particularly evident in the ways the concept has been re-energized in the context of debates about e-cigarettes." K. Bell, H. Keane, All gates lead to smoking: The 'gateway theory', e-cigarettes and the remaking of nicotine, *Social Science & Medicine* 119, 2014 (uploaded)
 Toxicity
 We ask that SCHEER clearly define the terms "toxicity" and "acute toxicity" to make the nomenclature clear especially concerning nicotine. Throughout the whole Opinion different and potentially conflicting standards for nicotine "toxicity" are used.
 Ref:
 Bell (2014). All gates lead to smoking: The 'gateway theory', e-cigarettes and the remaking of nicotine, *Social Science & Medicine*, Volume 119, 2014, <https://doi.org/10.1016/j.socscimed.2014.08.016>.

689	Woessner Julie, International Network of Nicotine Consumer Organisations (INNCO), Swiss based association	TERMINOLOGY	Page 19 / Lines 51-55 SCHEER objects to the use of the term "vaping", stating that it may imply that electronic cigarettes are a "healthy" alternative to cigarette smoking. "Vaping" is the vernacular terminology used by people who vape and should be used. There is absolutely no support offered for this statement and no indication that the word "vaping" implies much of anything in terms of risk or that nicotine users are being misled into believing that vaping is "healthy." In fact, we are concerned that the public misperceives the risks associated with vaping, with an increasing percentage of the public believing that vaping is equal to the risk of (or greater than the risk of) combustible tobacco use. In a 2020 study reporting on 2016-	Vaping has associations with "vapour", suggesting harmless exposure. Since the ToR ask for an assessment of exposure to e-cigarette aerosol and second hand exposure per se, the SCHEER considers the term vaping inappropriate.
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with 35 orgs all over the world and 15 from the EU		2018 data for six European countries, the majority of respondents perceived e-cigarettes to be equally or more harmful than combustible cigarettes. (abbreviated citation: Shannon Gravely et al., European Journal of Public Health, Volume 30, Issue Supplement_3, July 2020, document uploaded). This represents a failure of governments and public health to explain relative risks of vaping as compared to smoking.	
690	Froguel Alizee, Cancer Research UK, United Kingdom	TERMINOLOGY The term ‘vaping’ is simply the act of using an e-cigarette. We are not aware of any research that suggests it is intended to imply that the products are ‘healthy’. It is a term not only employed by users of the products but also the research community. In addition, some parts of the Committee’s opinion refer to e-cigarettes as “tobacco products” (for example in p62, 157 “In the US, they have become the most common tobacco products used by youth”). However, it is important to understand that in the US context, e-cigarettes and other electronic nicotine delivery systems (ENDS) have been deemed tobacco products since August 2016 primarily to allow the US Food and Drug Administration (FDA) to regulate them, as is the case for tobacco products.(1) Importantly, this rule allowed the FDA to implement a federal law to stop retailers from selling e-cigarettes, as well as cigars and hookah, to people under the age of 18. While Cancer Research UK understand and agrees with the intention behind the rationale to bring e-cigarettes under a robust regulatory framework to prevent unintended use among young people and those who do not smoke, we do not believe it is appropriate to extend the term “tobacco products” to include e-cigarettes more broadly. The WHO Framework Convention on Tobacco Control defines tobacco products as “products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing”. As e-cigarettes do not contain tobacco Cancer Research UK do not believe they should be referred to or classified as tobacco products.	Ref: Gravely et al (2020). European adult smokers’ perceptions of the harmfulness of e-cigarettes relative to combustible cigarettes: cohort findings from the 2016 and 2018 EUREST-PLUS ITC Europe Survey. doi:10.1093/eurpub/ckz215 Vaping has associations with “vapour”, suggesting harmless exposure. Since the ToR ask for an assessment of exposure to e-cigarette aerosol and second hand exposure per se, the SCHEER considers the term vaping inappropriate.

Reference:

1. US Food and Drug Administration. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products (81 FR 28973). 2016.

691 Robson Debbie, King's College London, United Kingdom
TERMINOLOGY page 19, line 51-55.

“The consumption of an electronic cigarette is often described as vaping. The SCHEER does not use this term, as it may imply, that the consumption of electronic cigarettes are a “healthy” alternative to cigarette smoking and consumers may misperceive risks associated with the use of electronic cigarettes. The SCHEER prefers to use the neutral “use (users) of electronic cigarette”.

It is unclear why the term ‘vaping’ could imply that electronic cigarettes are a ‘healthy’ alternative to cigarette smoking, as there is nothing in the terminology to suggest this. On the whole it is better to use a term that is in common parlance, particularly by those who use them.

Other terms are misused and are incorrect throughout the report - eg 'electronic cigarette smoking'.

Vaping has associations with “vapour”, suggesting harmless exposure. Since the ToR ask for an assessment of exposure to e-cigarette aerosol and second hand exposure per se, the SCHEER considers the term vaping inappropriate.

For other terms: the SCHEER has corrected all erroneous use of the word smoking and brought this in line with the general terminology used.