Results of the public consultation on SCHEER's preliminary Opinion on Additives used in tobacco products (Tobacco Additives II)

A public consultation on this Opinion was opened on the website of the Scientific Committees from 22 July to 22 September 2016. Information about the public consultation was broadly communicated to national authorities, international organisations and other stakeholders.

Twenty-two organisations and individuals participated in the public consultation, providing input to different parts of the Opinion, resulting in 214 contributions and nearly 1000 comments.

Most comments, by far, were from the tobacco industry, which disagreed with some aspects they considered too demanding to implement; on the contrary, other organisations and individual researchers expressed their appreciation to the SCHEER, recognising the difficulties in fulfilling such a complex mandate and positively commenting on the rationale followed by the SCHEER and on the indication that no animal testing should be performed *ex novo*.

The most frequent comments were related to comparative testing, which was not endorsed by the SCHEER in the preliminary Opinion. The claim was that this is the only way to answer to TPD Art 6 (6), according to which TI should assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR. Similar criticisms were directed toward the indication in the preliminary Opinion to carry out a pyrolysis study instead of smoke chemistry.

Tobacco industry also repeatedly criticised the preliminary Opinion for supposedly going beyond the Terms of References by examining properties such as 'attractiveness' as well as asking for the application of the precautionary principle.

The SCHEER provided an individual reply to each contributor. Each submission was carefully considered by the SCHEER and the preliminary Opinion has been revised in response to relevant comments.

More precisely, in the Final Opinion SCHEER clarified its position about comparative testing, specifying when it can be considered appropriate (e.g. in some human studies), but stating that at present, methodologies are not yet sensitive enough to discriminate between the very high background toxicity associated with tobacco with and without the additive. The SCHEER concludes that testing the effects of inhaling the pure additive and its pyrolysis products is the only meaningful way to comply with art. 6(2) of the TPD, i.e. to assess whether additives contribute to the toxicity or addictiveness of the products concerned.

For consistency with the terms of reference, the wording in the Final Opinion has been aligned with the TPD, avoiding the use of the term 'attractiveness' and replacing it with properties such as characterising flavour, facilitating inhalation and nicotine uptake, which fall under the TPD.

The SCHEER agreed that the reader might associate the precautionary principle with a risk measurement measure, although that was not the SCHEER's intention. For that reason, any reference to the precautionary principle has been deleted and indications were given for the assessor on the evaluation of the collected available and new data on the additive and its pyrolysis products in case uncertainties could not be clarified by new testing.

The many papers provided by the tobacco industry were checked and the literature has been accordingly updated with relevant publications. However, in most cases they were not considered to have provided any additional information or any information relevant enough to require amending the Opinion.
In the final Opinion, some changes were included to address specific comments and editorial changes were made to address comments pointing out possible misunderstandings.
The SCHEER would like to thank all contributors for their comments and for the references provided during the public consultation.

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.

Scientific Committees
on Consumer Safety
on Health, Environmental and Emerging Risks

Comments received during the public consultation on the SCHEER preliminary opinion on Additives used in tobacco products, Opinion 2 (Tobacco Additives II)

No	Name of individual/organisation	Table of contents to which comment refers	Submission	SCHEER's response
1.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	ABSTRACT	The Opinion states that comparative toxicity testing strategies are not considered suitable. However, comparative testing (CT) is necessary to comply with Art.6TPD2 (A6), which requires assessment of whether additives contribute to or increase "toxicity or addictiveness… to a significant or measurable degree". The most appropriate way to test a burnt tobacco additive is under conditions of use (in a cigarette). This accounts for interactions between compounds, possible additive effects and the impact of complex mixtures. The examination of whether an additive results in a characterising flavour equally presupposes CT to assess to what degree the additive affects the flavour of the cigarettes or RYO. It is impossible to examine whether an additive "facilitates" inhalation or nicotine uptake without CT. Finally, CT is required to assess whether the use of the additives has the effect of increasing CMR properties. In short, without CT the studies would not comply with A6. CT would better fulfil SCHEER's objective that "test outcomes should be relevant for tobacco smoking…related to actual human exposure…and to tobacco-induced diseases" (p4:37-39), and A6's requirement that studies "take into account the intended use of the products", as it involves testing the additives in the tobacco product rather than in isolation. It is not the case that the assay lacks	Strictly speaking, Comparative Testing (CT) of an additive in the tobacco matrix compared to the tobacco matrix without the additive is the only way to comply with Art.6TPD2 (A6), to assess whether additives <u>increase</u> "toxicity or addictiveness ... to a significant or measurable degree". However, as the SCHEER clearly stated in the preliminary Opinion the high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that if methodologies that are sensitive enough would become available, they could be used. The SCHEER indeed stated in the Preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. The two exceptions (human studies for detecting characterising flavour and inhalation facilitation are now highlighted in the section regarding CT, but also cited in the abstract and in chapter 4 (Opinion). On the other hand, Article 6(2) of the TPD states that: *Member States shall require manufacturers and importers of cigarettes and roll-your-own tobacco containing an additive that is included in the priority list provided for in paragraph 1, to carry out comprehensive studies, which shall examine for each additive whether it:*

			discriminative power, but that additives are present at such low levels compared to the tobacco matrix that their influence on the toxicity, addictiveness or CMR properties is insignificant. This is what the enhanced reporting is intended for–whether a product with additives is more toxic, addictive or has increased CMR properties than without. A6 para.2(a),(d) state that the studies are to ascertain whether the increase is "to a significant or measurable degree." Where the increase is not, there is no requirement to measure under A6.	*(a)* ***contributes to the toxicity or addictiveness of the products concerned****, and whether this has the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree;* *(b) results in a characterising flavour;* *(c) facilitates inhalation or nicotine uptake; or* *(d) leads to the formation of substances that have CMR properties, the quantities thereof, and whether this has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree.* In order to comply with art. 6(2) of the TPD, that is to assess whether additives **contribute** to the toxicity or addictiveness of the products concerned, testing the effects of inhaling the pure additive (and its pyrolysis products) is the only meaningful way. In this paradigm, the comparator or reference is inhaling air/zero toxicity. Literature data show that the additive and its pyrolysis products can have significant toxic and addictive effects that may result in serious health problems. The issue is related to the **mixture toxicity** for which the additive model [as opposed to synergistic and antagonistic ones] and a component approach, is proposed as the **most pragmatic way** to asses toxicity of mixtures, unless specific data are available indicating that a different model has to be used. In this specific case the effect of inhaling the additive itself, and its relevant pyrolysis products, is the **contribution of the additive to the total toxicity** of the tobacco smoke. Although there will potentially be synergistic or antagonistic effects of the additive and its pyrolysis products within the smoke matrix, as well as pyrosynthesis reactions, the net effect of all these contributions is too complex to study and assess with the currently available methodologies. The current state of the art only allows for assessing other than additive effects for very simple mixtures, not for mixtures of thousands of components such as tobacco smoke. As a consequence the SCHEER is aware that the possible interactions generated by reactions among ingredients can be underestimated, but moving ahead pragmatically is the only way to go.

				Therefore, **the SCHEER does not agree** with the TI statement "*It is not the case that the assay lacks discriminative power, but that additives are present at such low levels compared to the tobacco matrix that their influence on the toxicity, addictiveness or CMR properties is insignificant*", because it is the high toxic potential of the tobacco matrix that makes experimentally problematic to study the influence of a single additive on the toxicity, addictiveness or CMR properties of the matrix, and not so much the low quantity of additives present in the matrix. In addition, the SCHEER reiterated the rationale that the results of comparative toxicity testing strategies, where differences in the effect of the tobacco product with and without the additive are evaluated, cannot be generalised to all products and brands, having a different composition with respect to tobacco type, blend and additives. With CT, due to the lack of discrimination, in almost all of the cases, the conclusion will be that there is **no measurable increase**. In that case, all testing will be meaningless.
			2.2 states that "In the tobacco matrix, either the intact additive or its pyrolysis products may react with other additives, tobacco- or smoke components (pyrosynthesis)." (p.14:22-24) This further validates the use of CT, together with the requirement under A6 that studies be relevant to tobacco smoking, as CT will include such reactions which are relevant at the stage of consumption. The Opinion claims that the results of a CT "cannot be generalised to all products and brands…Comparative studies are also not endorsed to study the effect of additives on addictiveness and inhalation facilitation" (p4:43-45).	For this reason, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products".
			SCHEER's stance on comparative testing contradicts that of one of its external experts. Kienhuis et al, 2016 [11], co-authored by Dr Talhout states that "Comparative testing is the only way to assess whether additives increase the overall toxicity of	There is no contradiction: the statement is true but, at present, methodologies are not available that are sensitive enough to discriminate between the very high background toxicity associated with tobacco with and without the additive.

			tobacco products, as is required in the new TPD. This approach is also proposed by the FDA…" The proposed alternative testing of the pure additive does not resemble human exposure, thus undermining SCHEER's requirement that studies "take into account the intended use of the products". Whilst the stepwise strategy is appropriate in this context, the current proposition has the following flaws: 1. Lack of comprehensive and finite list of appropriate tests for each step. This presents an issue with the timeframe as the industry is unable to plan an appropriate testing forecast without knowing what tests are required. Studies may need to be conducted in parallel to meet the timeframe. 2. While the Opinion proposes tests on the unburnt form, A6, p.3 requires taking account of "the intended use of the products concerned and examine in particular the emissions resulting from the combustion process involving the additive concerned." This proposal is neither consistent with nor required under A6.	This concept has been made clearer in the text of the revised Opinion. This is outside the remit of our mandate. The SCHEER was not asked to give detailed protocols but to advise the Commission on a possible framework to help the MS in asking and Tobacco Industry (TI) to present sound data; in particular the ToR states: *The Committee is asked to advise the Commission on the* ***type and criteria for comprehensive studies*** *that should be requested*. It has been clarified upfront in the text. Regarding the timeframe, the possibility exists that different steps can be run in parallel. For this reason, the Opinion also proposes tests with the pyrolysis products.
2.	COMBES, ROBERT, CAVENDISH CONSULTING, robert.d.combes@gmail.com, United Kingdom	ABSTRACT	 scheercombesballsCPTE_1.doc	Thank you for the comment letter. Some statements, however, like: *only additives with a positive proven human health benefit, as demonstrated by agreed methods, including volunteer studies, where feasible, should be permitted. Adoption of such a strategy would reduce the volume of testing required, and would eliminate the use of additives being used to encourage smoking, in line with the general policy of bans on advertising and dangerous to health product labelling* are outside of the ToR, which the SCHEER must adhere to in answering **questions asked by the Commission.** The SCHEER disagrees with the comments: *the recommendation by the committee to discourage human studies is highly regrettable.* Indeed it is questionable to encourage studies in

				which the test item is surely highly toxic. In addition the SCHEER is not saying they are not allowed. For some end-points they could be indeed the only way of testing, as stated in the preliminary Opinion. The issue has been expanded to increase clarity in the revised version. Other comments suggesting clarification of the text have been addressed.
3.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, javier.martinez@jti.com, Other	ABSTRACT	p.4, l.10 Please delete "or otherwise"; l.11: Please add the word "may" before "promote". p.4, l.11 Please remove: Additives "promote addiction." p.4, l.12 Please remove the notion of a precautionary principle as it is inconsistent with the TPD2, which does not allude to the baffling notion that a "reasonable suspicion" should be the basis for decisions about the use of additives. On the contrary, Articles 6(2) and 7(9) require such decisions to be based on concrete evidence, i.e., findings that an additive increases the "addictiveness" of a product "to a significant or measurable degree." p.4, l.16 + p.5 l. 8 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Thus, the Committee exceeds the TPD2 and its Terms of References when examining whether additives increase "attractiveness". The SCHEER precisely points to the only two references	The text has been revised accordingly. Having inserted "may", the potential for this action is included, in line with the SCENIHR Opinion (2010). The Opinion refers to the precautionary principle (PP) to indicate that in case of uncertainty in the positive evidence from comprehensive data for the 'significant and measurable contribution to the toxicity or addictiveness of the products concerned' or for 'the formation of substances that have CMR-properties' (Article 6.2), risk management measures should be taken in accordance with article 7 of the TPD. But the SCHEER agrees that the text could be misinterpreted as giving indication on risk management measures which is not included in the SCs mandate. For this reason, there is no reference to the precautionary principle (PP) but the SCHEER gives advice to the assessor on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points. P. 4: On p. 4, the SCHEER used the word attractive to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On p. 8, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

			to "attractiveness" provided in the TPD2. Tellingly, these references clarify that the industry is not compelled to test for "attractiveness", and highlight the lack of any basis on which the Commission or Member States may take action with respect to "attractive" additives, except in the very limited context of additives that result in a characterizing flavor. Neither the SCHEER nor the Commission has authority to amend the TPD2. Consequently, the reference regarding "attractiveness" is irrelevant and should be removed.	The term attractiveness has been replaced when relevant with the terms used in the ToR: facilitating inhalation, resulting in characterizing flavour or increasing nicotine uptake.
			p.4, l.32-33 The concept of "addictiveness" needs to be (i) adequately defined and (ii) objectively measureable before it may be considered as a basis for regulation. 6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion.	The term addictiveness has been further defined, although it was already specified in the previous Opinion (Tobacco I) which definition the SC endorsed.
			p.4, l.33 Please amend: "mechanisms underlying addictiveness are poorly understood." Contrary to SCHEER's assertion, the mechanisms underlying "addictiveness" of the final tobacco product are not fully elucidated. p.4, l.39-46.SCHEER suggests that comparative studies are not endorsed due to the lack of discriminative power and inability of generalization from one specific testing blend to others. Nonetheless, the criteria/evaluation (to ban an additive if any CMRs occur in pyrolysates) proposed by SCHEER cannot be endorsed as a pure additive pyrolysis study represents simply a model study to estimate possible smoke constituents in cigarette mainstream smoke but far from the actual	The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). The SCHEER modified this sentence to clarify that these mechanisms are not fully elucidated. The text was amended including 'some', addressing the comment that only some mechanisms are known at present.

			conditions. As SCHEER noted, "Most importantly, the test outcomes should be relevant for tobacco smoking". Thus, SCHEER should not suggest that absolute criteria (Step 2) and should endorse the comparative testing to assess the effect of each additive and their pyrolysates under the actual condition of use. The guidance provided by SCHEER is inconsistent with the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation.	For CT please see the answer n°1 to comment n°1 (page 2) The SCHEER indicated that the test outcomes should be relevant for tobacco smoking, meaning that, e.g. for toxicity testing the inhalation route is much more relevant than the oral one or that, whenever a pyrolysis study is carried out, the temperature and other experimental conditions should be those typical of smoking.
4.	Loft, Pia, Scandinavian Tobacco Group A/S, pia.loft@st-group.com, Denmark	ABSTRACT	Please see the attached paper which contains our comments to the report with references to line numbers and sections of the text.  Opinion_on_SCHEER_report.docx	Please see the answers (in red) to the 6 comments included in the attached file.
5.	Simms, Liam, Imperial Tobacco Limited, Liam.Simms@uk.imptob.com, United Kingdom	ABSTRACT	We welcome the opportunity to comment on this Preliminary Opinion 2. The aim of the Directive is to harmonise Members States' laws to genuinely improve the conditions for the establishment and smooth functioning of the internal market. Any use of this Preliminary Opinion 2 by Member States in their broader regulatory/enforcement activities to set national thresholds/banning of additives will lead to a	This is outside the SCHEER ToR.

			patchwork of different ingredients regulations in different Member States. This could lead to the potential ban of individual additives in tobacco products marketed legally in some member states but not the rest of the EU. There are areas in the Abstract which go beyond Directive 2014/40/EU (the 'Directive'): Lines 6-10: Art. 6 of the Directive does not include any provision which allows the Commission to: (i) specify to manufacturers/importers (beyond the scope of Articles 6.2 and 6.3) the type and criteria for the comprehensive studies or the most suitable methodologies manufacturers/importers must utilise when carrying out comprehensive studies; or (ii) Set out a reporting template for manufacturers/importers. Lines 10 – 13: Due to the known health risks of smoking, we agree with SCHEER that a risk-benefit analysis is not the appropriate paradigm for assessing additives in tobacco products. Lines 12-13: The statement on the precautionary principle is inappropriate and should be deleted as it is a preventative decision-taking approach to risk management. Tobacco has its own naturally occurring CMR properties (both in non-combusted and combusted form). Additives are studied and assessed so as not to increase the CMR properties of a consumed tobacco product. This methodology satisfies the requirements of Articles 6.2 and 6.3 for following reasons: - Art. 6.2(a) the Directive states "…effect of increasing the toxicity or addictiveness of any of the	The points the commenter is referring to are included in the ToR from the Commission, to which SCHEER has to comply with. The ToR is copied below: *The Committee is asked to advise the Commission on the **type and criteria for comprehensive studies** that should be requested from manufacturers to assess the relevance of the individual additives, considering inter alia the **knowledge gaps identified in point 1** above and the interaction of the additive with other additives/ ingredients.* *Advice is also sought on the **most suitable methodologies** to be used (including a structure of the reports that can be peer reviewed).* The SCHEER would like to thank you for the positive comment. The Opinion refers to the PP to indicate that in case of uncertainty in the positive evidence from comprehensive data for the 'significant and measurable contribution to the toxicity or addictiveness of the products concerned' or for 'the formation of substances that have CMR-properties' (Article 6.2), risk management measures should be taken in accordance with article 7 of the TPD. But the SCHEER agrees that the text could be misinterpreted as giving indication on risk management measures, which is not included in the mandate. For this reason in the revised version, there is no reference to the PP but an advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of

			products concerned to a significant or measurable degree." It is the sole responsibility of manufacturers/importers to carry out comprehensive studies, to do so effectively requires a combination of biological end points within a systematic weight of evidence approach. - Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof, and whether this has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree". - Art. 6.3 states "Those studies shall take into account the intended use of the products concerned and examine in particular the emissions resulting from the combustion process involving the additive concerned…." Which ensures that any study applied is representative of the intended conditions of use of the tobacco product. Lines 22-23: We agree that no validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. Lines 14-15: In seeking a pragmatic and efficient approach to additive assessment, we believe a weight of evidence approach which includes reference to comparative toxicology as well as the use of appropriate validated studies will achieve this. Lines 47-48: We agree with SCHEER on the avoidance of animal and human studies, but add that where such	validated studies for some end-points. For this reason, The SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". The application of a WoE was already present in the preliminary Opinion. The SCHEER advised to provide any available data. This means that TI can provide also the comparative testing studies if carried out before this Opinion was adopted. The SCHEER meant that no new animal studies should be conducted, but any data that was already available should be included in the dossier and analysed. It will be then the task of the assessor to give the right weight to any study (including CT) in a WoE approach. Therefore there is no disagreement between the SCHEER and TI.

			studies have been completed the data is utilised where scientifically relevant. In this Preliminary Opinion SCHEER outlines several hypotheses, not validated by scientific evidence, and contradicts available research (Mueller et al. 2000). We support evidence based on robust methods and credible scientific research, on which valid assessment can be based.	This has been further clarified in the revised version.
6.	Erich, Erichsen, Ministry of Health, Denmark, eer@sum.dk, Denmark	ABSTRACT	The Danish attitude to SCHEER: "Preliminary Opinion on Additives used in tobacco products (opinion 2) Tobacco Additives II" Denmark welcomes the attempt to find a joint approach to reports submitted under Article 6, including, among other things, as an important contribution to decisions that may be made under Article 7 – including a prohibition against the use of certain ingredients. In this connection, Denmark finds it important that the joint approach will be based on fulfilment of the Directive's explicit methodology and requirements and will be based on an unbiased and scientific approach to the subject. On the basis of this, the draft gives rise to a number of questions: • Will the suggested pyrolysis test of the pure substance, e.g. as mentioned on p. 21, line 5 ff, be sufficient to ensure a fully reliable knowledge of whether it "leads to the formation of substances that have CMR properties, the quantities thereof, and whether this has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree.", as stipulated in Article 6.2(d)? Refer here that the formation of substances with CRM properties may arise from the reaction between the added substances. • Will the suggested method/test in itself be adequate to provide the knowledge base required in order for the member states to prohibit the	Thank you for the positive comment. However, based on the many comments received on this issue, the SCHEER realized that the text could be misinterpreted as giving indication on risk management measures (outside the remit of the SCHEER mandate). For this reason in the revised version, there is no reference to the PP but advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points. The SCHEER can agree that reactions among tobacco products components as well as the possible interaction leading to more-than-additive effects will not be identified by testing the single additive/ ingredient. On the other hand, CT at the moment cannot be endorsed (see answer to comment n°1) since it could hardly provide the appropriate sensitivity to see any differences. Therefore this is the only pragmatic way to propose any framework. Some clarification has been added to the text in the revised version. The SCHEER cannot answer this question; the banning is a risk management measure and it is outside the remit of the SC.

			marketing of tobacco products as set out in Article 7, 9, which reads: ”CMR properties of a tobacco product at the stage of consumption to a significant or measureable degree.”?	
			• Is it realistic for companies to comply with the suggested procedure about size and content of their reporting as set out in Article 6 within the Directive’s deadline of 18 months?	The SCHEER considers it possible, also in view of some comments sent by TI, in which it is stated that before using an additive TI carries out testing to evaluate its safety both as a single chemical as well as in comparative testing: therefore TI should not be worried, since most of the data indicated in the step procedure described in the Opinion are available. As clearly stated in step 1 and step 2 all the available data should be presented. In case they are sufficient to the evaluation, no testing is needed (no step 3 activity).
			• Is the demand for reporting of the effect on ”attractiveness” in accordance with Article 6 of the Directive, e.g. as mentioned on p. 16, line 14 ff?	On p. 4, the SCHEER used the word attractive to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On p. 8, it has been replaced by “properties facilitating inhalation or resulting in characterising flavour”.
			To ensure the same understanding it should be the Member States that should determine "keywords", "dates" and “search strategy" to ensure uniformity, that all relevant literature is considered and a common framework of understanding. In addition, there should be a clear announced line around when an additive has a "concern level" (p. 20, line 34), additive contributes to toxicity (p. 20, line 39, a)) or the additive has CMR properties / increases CRM properties on a significant or measureable degree (when is CRM features so low that a health authority may approve / accept them) (page 20, line 44-46, d)).	This is outside the SCHEER ToR. However, the situation is similar to the one related to evaluation of other kind of products which could sometimes differ in different MS.
7.	No agreement to disclose	ABSTRACT	It should be noted that the pyrolysis cannot take place by consuming of smokeless tobacco products, e.g. snuff or chewing tobacco, and therefore the	This is a risk management issue; outside of the scope of the Opinion and the remit of the SCHEER.

	personal data		CMR-characteristics cannot be incurred. A snuff is for consumers non-consumable without additives therefore a prohibition of additives will consequently means a total ban on snuff. For this reason the prohibition of additives in smokeless tobacco products is excepted in TPDII. In case of consuming pipe tobacco the smoke will not be inhaled into the lungs but only be puffed. Pipe tobacco is consumed mainly by elderly people who expect a flavoured and moist tobacco. Therefore, the ban of additives in pipe tobacco will consequently lead to a ban of pipe tobacco. For this reason the ban of additives in smokeless tobacco products is excepted in TPDII.	
8.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	ABSTRACT	We thank SCHEER for having considered our comments on its opinion 1. We also welcome the Commission's initiative to provide non-binding guidance on how to conduct studies under Art. 6 TPD and the opportunity to comment on this initiative. Since the studies "shall assist the Commission and Member States in taking the decisions pursuant to Article 7" (Art. 6(4) TPD), i.e., whether or not to limit or ban the use of additives, opinion 2 should be strictly consistent with this provision. To provide useable guidance, SCHEER needs to amend opinion 2 in particular (i) to provide for comparative testing and (ii) so that the proposed stepwise approach based on DKFZ allows for a weight of evidence approach and includes in step 3 smoke chemistry and in vitro tests (see DIN and Health Canada discussed in 2.4.3.4).	For CT, please see the answer n°1 to comment n°1. The application of a WoE was already present in the preliminary Opinion (page 19 in section 3.4.1.1 Collection of literature data). SCHEER advised to provide any available data. This means that TI can provide also the comparative testing studies if carried out before this Opinion was adopted. SCHEER meant that no new animal studies should be conducted, but any already available data should be included in the dossier and analysed. It will be then the task of the assessor to give the right weight to any study (including CT) in a WoE approach. Therefore there is no

				disagreement between the SCHEER and TI. This has been further clarified in the revised version.
			The DKFZ proposal was made in 2010 when no EU legislation existed in this area. However, the EU legislator, with the TPD, has decided to regulate in a way diametrically opposed to DKFZ's proposal. DKFZ finds it inappropriate that "the additives should be admixed to the tobacco product and the tobacco smoke analyzed for changes in the degree of toxicity" and that an additive be banned "only if the additive increases the toxicity of the tobacco smoke" as assessed in this manner (p. 45). However, the EU legislator decided this to be right approach (Art. 6(2),(3) TPD) and the decisive criterion (Art. 7(9) TPD). Using DKFZ's proposal as a basis for opinion 2 is not consistent with Art. 6(2) and Art. 7(9) TPD.	The SCHEER step procedure took inspiration from the German Cancer Research Centre, but then the SCHEER developed its own procedure. In case the comments refers to SCHEER position (similar to DKFZ) not to consider CT carried with currently available methodologies suitable to discriminate between tobacco product toxicity with and without an additive, please see the answer to comment n°1.
			If the stepwise evaluation stops already at step 2, it is not possible to determine whether an additive increases the toxic or addictive effects or the CMR properties "at the stage of consumption to a significant or measureable degree" (Art. 7(9) TPD). It is premature at step 2 to make TPD-compliant decisions about the additive and the evaluation should always proceed to step 3. We therefore suggest to replace the phrase "In case (…) evaluation possible," (p. 4, l. 25-26) with "In step 3," and ", all of which could be done in Step 3" should be deleted.	If the data set of available data is robust enough to take decisions, there is no need to go for further testing as described in step 3.
			Also, if comparative paradigms are excluded, it would not be possible to determine if an additive increases to a significant or measurable degree the afore-mentioned effects. Therefore, we suggest to replace the phrases "Furthermore, (…) considered"	For CT issue, please see the answer n°1 to comment n°1.

			(p. 4, l. 39-46) by "After completion of all three steps, the evidence obtained in all three steps should be assessed and weighted (weight of evidence approach)" (see section 2.4).	
			Opinion 2 should not only foresee the possibility to ban but also to limit the use of additives as specifically provided by Art. 7(9) TPD ("containing additives in quantities that increase") and Art. 7(11) ("to set maximum content levels for those additives").	The decision to ban or limit the use of an additive is outside the remit of the SC.
			SCHEER should also reconsider its references to the precautionary principle in the phrases "As tobacco additives (…) full force" (p. 4, l. 10-13) and its statements regarding the burden of proof. While the precautionary principle plays a role when discussing how to deal with a risk (as DKFZ does), it has no relevance when the regulator has already taken this decision. In the latter case, the regulator's decisions on how to apply the precautionary principle should be respected (see section 2.4). We encourage SCHEER to focus its opinion 2 on how to assess risks, which is SCHEER's mandate, and not how to manage them (see section 1.2).	The SCHEER agrees that the text could be misinterpreted as giving indication on risk management measures, which is not included in the mandate. For this reason, in the revised version, there is no reference to the PP but the SCHEER gives advice to the assessor on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points.
			Where no validated methods exist, we encourage SCHEER to trigger relevant research. We would welcome an opportunity to contribute to this research. In the meantime, we will carry out and report on studies using the best currently available methods.	Reporting on research needs was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted.
			Since attractiveness is not a relevant criterion under Art. 6 and 7 TPD, it should be deleted throughout opinion 2.	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

9.	Gundersen, Alex, AG SNUS Aktieselskab, , Denmark	ABSTRACT	p.8 line 27-29,p13 line 11 ff, p 16 line 15 ,p 21 line 17 ff, p 23 section 2.4.2.3, p24 line 5ff p.25 line 26 ff.  DK_-_SCHEER.docx	See the answers (in red) in the attached file.
10.	Stoddart, Gilly, PETA International Science Consortium Ltd., GillyS@piscltd.org.uk, United Kingdom	ABSTRACT	PISC agrees that the precautionary principle is a more appropriate paradigm than a risk-benefit analysis for assessing tobacco additives and welcomes the committee's statement, in the abstract of its opinion, that animal studies are not endorsed - for ethical reasons. As stated, the EU policy to ban animal studies for chemicals to be used in voluntary products indeed applies in this case.	The SCHEER would like to thank for the positive comment. However, based on a number of comments received, the SCHEER realized that the text could be misinterpreted as giving indication on risk management measures, which is not included in the mandate. For this reason in the revised version, there is no reference to the PP but an advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points.
11.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	ABSTRACT *The same comment was submitted by the same commenter also for the following chapters:* *2.1 Introduction* *2.4.1.2 Evaluation* *2.4.2.3*	The report of SCHEER aims to present an approach for the assessment of tobacco additives. We have serious concerns on the scope, alleged findings and recommendations of the Preliminary Opinion and would like to raise some in-principle and critical remarks as expanded on below. The scope and objective in the preliminary opinion of SCHEER should be adapted to be in line with the corresponding requirements in directive 2014/40/EU. Several times in its report SCHEER misinterprets provisions of Directive 2014/40/EU: • the methodology proposed by the SCHEER is based on an apparent misreading of the relevant provisions of TPD2 and, if followed by tobacco manufacturers or mandated by competent authorities, would (i) preclude the use of individual additives outright, including those essential for the	The SCHEER ToR was to 'advise the Commission on the **type and criteria for comprehensive studies** that should be requested from manufacturers to assess the relevance of the individual additives'. Therefore the SCHEER based the Opinion on scientific ground; the SCHEER was not asked to evaluate the consequences due to the risk management measures taken afterwards.

		Evaluation *2.5.1 Carob bean* *2.5.14 Sorbitol* *2.5.9 Guar gum*	manufacture of products; (ii) discriminate between different tobacco varieties and (iii) prevent differentiation. All outcomes that are inconsistent with the objectives and requirements of TPD2; • the SCHEER report also places extensive reliance on flawed concepts, such as the potential "attractiveness" of additives, despite this not being mentioned in the Commission's terms of reference and it not being a relevant consideration for the purposes of these provisions of TPD2.	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
			• the concept of "addictiveness" needs to be (i) adequately defined and (ii) objectively measureable before it may be considered as a basis for regulation. 6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion; In this context we propose to amend that "mechanisms underlying addictiveness are poorly understood." Contrary to SCHEER's assertion, the mechanisms underlying "addictiveness" of the final tobacco product are not fully elucidated;	The concept of "addictiveness" has been defined again in the Final Opinion, although a clear definition was already stated in Opinion I. The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke).
			• the notion of a precautionary principle as it is inconsistent with the TPD2, which does not allude to the baffling notion that a "reasonable suspicion" should be the basis for decisions about the use of additives. On the contrary, Articles 6(2) and 7(9) require such decisions to be based on concrete evidence, i.e., findings that an additive increases the "addictiveness" of a product "to a significant or	The SCHEER agrees that the text could be misinterpreted as giving indication on risk management measures, which is not included in the mandate. For this reason in the revised version, there is no reference to the PP but an advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points

			measurable degree." The SCHEER report should be modified to corresponds exactly with the provisions of the directive.	 The wording has been changed to be fully consistent with ToR and the TPD.
12.	Bosse, Andrea, DVAI - The Association of the German Flavour Industry, info@dvai-dvrh.eu, Germany	ABSTRACT	The Preliminary Opinion Additives used in tobacco products (Tobacco additives II) provides an approach for the assessment of tobacco additives. The Association of the German Flavour Industry would like to give some general remarks regarding this report and the extracted recommendations. Our remarks do not provide a comprehensive opinion regarding this preliminary opinion, but concentrate on certain main points, especially the toxicity assessment and characterizing flavour. • The methodology proposed by the SCHEER is based on a misreading of the relevant provisions of Directive 2014/40/EU and, if followed by tobacco manufacturers or mandated by competent authorities, would (i) preclude the use of individual additives outright, including those essential for the manufacture of products; (ii) discriminate between different tobacco varieties and (iii) prevent differentiation. All outcomes are inconsistent with the objectives and requirements of Directive 2014/40/EU. • The SCHEER opinion issues the potential "attractiveness" of additives. Attractiveness is not mentioned in the Commission's terms of reference and is in our opinion not a relevant consideration for the purposes of the provisions of Directive 2014/40/EU.	 The SCHEER ToR was to 'advise the Commission on the **type and criteria for comprehensive studies** that should be requested from manufacturers to assess the relevance of the individual additives'. Therefore the SCHEER based the Opinion on scientific ground; the SCHEER was not asked to evaluate the consequences due to the risk management measures taken afterwards. Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
13.	Ureel, Ludwig, British American Tobacco, ludwig_ureel	2 SCIENTIFIC RATIONAL	In a number of subsections falling under heading 2 (namely 2.1., 2.2, 2.3, 2.3.4, 2.4.1.1, 2.4.2, 2.4.3.1, 2.4.3.6, 2.5.1, 2.5.2, 2.5.6, 2.5.7, 2.5.9 and 2.5.14) SCHEER notes specific or general concerns regarding the alleged attractiveness of	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

	@bat.com, United Kingdom		additives. However, apart from there being no scientifically valid method for assessing attractiveness, SCHEER acts beyond the scope of both its Terms of Reference and Article 6 TPD2, given that attractiveness is not listed among the outcomes listed in Article 6.2(a)-(d) TPD2, which the studies are meant to assess.	
14.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland., Javier.Martinez@jti.com, Other	2 SCIENTIFIC RATIONAL	According to TPD2 article 6 (2), Member States shall require manufacturers and importers of cigarettes and roll-your-own tobacco to carry out comprehensive studies on additives that are included in the priority list adopted by the EC Implementing Decision (EU) 2016/787. The studies shall examine for each additive whether it increases toxicity or "addictiveness", leads to the formation of substances with CMR properties in any of the products to a significant or measurable degree; results in a characterizing flavor; facilitates inhalation or nicotine uptake (the Properties). The information produced from said comprehensive studies shall assist the Commission and Member States in taking the decisions, pursuant to Article 7, to ban the use of a given additive. Nonetheless, Member States shall not prohibit the use of additives which are essential for the manufacture of tobacco products, provided those additives do not result in a product with a characterizing flavor and do not increase to significant or measurable degree the "addictiveness", toxicity or the CMR properties of the tobacco product. Notwithstanding the above, the SCHEER's "Preliminary Opinion on Additives used in tobacco products" (Opinion 2) seems to propose a testing methodology which will result in the ban of several additives, even when they do not result in a product with a characterizing flavor and do not increase to significant or measurable degree the addictiveness, toxicity or the CMR properties of	The SCHEER ToR was to 'advise the Commission on the **type and criteria for comprehensive studies** that should be requested from manufacturers to assess the relevance of the individual additives'. Therefore the SCHEER based the Opinion on scientific grounds; the SCHEER was not asked to evaluate the consequences due to the risk management measures taken afterwards. As a consequence, with the currently available methodologies the SCHEER could not consider CT sensitive enough to comply with the requests of the TPD in article 6(2) and 6(6).

			the tobacco product. For example, SCHEER recommends that a reasonable suspicion of toxicity is sufficient to deny approval of such a substance, regardless if it meets the criteria provided by Article 7 of the TPD2. Furthermore, the individual testing of the pure additive, proposed in the Opinion 2 is not in line with the TPD2 requirements, as in order to understand if the quantity of the additive used increases the toxicity, addictiveness and CMR properties, products have to be tested under conditions of use. Currently, there are no internationally accepted test methods to be used. Validated test methods addressing certain biological effects, such as "addictiveness" do not yet exist. The SCHEER's Opinion 2 proposes to conduct pyrolysis tests, however, this does not provide any clarity on the methods, but instead states that no validated methods are available for the pyrolysis of tobacco additives. Finally, in addition to the testing parameters of the TPD2 Article 6, the SCHEER's Opinion 2 seems to have also added a new one under the concept of "Attractiveness" which is in no way defined or regulated under the TPD2. Given the lack of clarity and absence of certain test methods described above, as well as lack of scientific evidence, it is highly unlikely that the results of these studies will, at least initially, provide data of sufficient quality to support any prohibition of tobacco products containing additives in quantities that increase the properties of a tobacco product at the stage of consumption to a significant or measureable degree, according to the TPD2 article 7 (9).	The SCHEER recommended evaluating all the available data based on a WoE approach. Only in case there is still a high level of uncertainty, which cannot be solved/reduced with further testing, does the SCHEER advise that risk reduction measures be immediately applied in accordance with the precautionary principle and Article 7 of the TPD. The issue has been clarified within the Opinion. The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. At other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

15.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2 SCIENTIFIC RATIONAL	Since the enhanced reporting requirements in Art. 6 TPD apply only to cigarettes and roll-your-own and not to all tobacco products, we suggest changing the title of opinion 2 from "Preliminary Opinion on Additives used in tobacco products (Opinion 2) Tobacco Additives II" to "Preliminary Opinion on Additives used in cigarettes and roll-your-own tobacco (Opinion 2) Cigarette and Roll-your-own Additives II". This would be aligned with the terminology used in the Commission Implementing Decision (EU) 2016/787 of 18 May 2016 laying down a priority list of additives contained in cigarettes and roll-your-own tobacco subject to enhanced reporting obligations, adopted pursuant to Art. 6 (1) and to which opinion 1 contributed. Otherwise, we see the risk that the title could be misleading. It could be misunderstood to mean that the proposed testing methods would also be relevant for tobacco products other than cigarettes or roll-your-own (see Art. 2(5) TPD).	The application domain of the Opinion (cigarettes and roll-your-own tobacco) has been made clear since the first line of the Abstract. Changing the name of the Opinion is considered not relevant and possibly misleading, since this is the second Opinion in a series. SCHEER will reiterate that the Opinion is applicable only to cigarettes and roll-your-own tobacco in other parts within the text.
			Per the Terms of Reference, SCHEER's opinion 2 should "advise the Commission on the type and criteria for comprehensive studies that should be requested from manufacturers to assess the relevance of the individual additives" and on "the most suitable methodologies to be used." SCHEER has therefore been asked to advise on how to assess risks, not how to manage them. However, while SCHEER makes proposals on how to manage risks (see further comments in section 2.1), we lack guidance on how to assess them, namely advice on "the type and criteria for comprehensive studies". We kindly request that the Committee amends its opinion to provide the guidance which the industry needs in order to comply with Art 6 TPD in the limited timeframe provided for (18 months as of January 1st, 2017, to manufacture prototypes,	The SCHEER disagrees. The SCHEER gave as far as possible the type and criteria for comprehensive studies to be requested. However, based on the comments received, the SCHEER realised that the text could be misinterpreted as giving indication on risk management measures, which is not included in the SCs mandate. For this reason in the revised version, there is no reference to the PP but an advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. The SCHEER also gave indication that in order to evaluate data for risk assessment a WoE approach should be used. Only when there is still a high level of uncertainty which cannot be solved/reduced with further testing does the SCHEER advise that risk reduction measures be immediately applied in accordance with the precautionary principle and Article 7 of the TPD. Some sentences have been rephrased to avoid misinterpretation. The SCHEER was not requested to give detailed protocols for

			carry out the testing and draft the reports). Where no validated methods exist (as highlighted by SCHEER at, e.g.: p. 4, l. 22-23 and p. 66, l. 24-25 ("no validated methods exist for the determination of pyrolysis products from tobacco additives"); p.4, l. 32-33 and p. 66, 32-35 ("addictiveness should be assessed, an effect for which no validated tests are available"); and, similarly, at p. 24, l. 47; p. 25, l.3; p. 34, l. 25-27; p. 30, l. 1-2; p. 54, l. 17), we encourage SCHEER to trigger the development of relevant research, in line with the Committee's expressed interest at p. 69, l. 25-26 ("It is advised that independent bodies or organisations begin conducting relevant research"). We would welcome any opportunity to contribute to this research and method development. In the meantime, we will carry out and report on studies using the best currently available methods.	specific studies and whenever possible referred to test guidelines or other approaches already adopted in areas other than tobacco products. Reporting on research needs was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted. Some indication is also given at the end of chapter 4.
16.	Schwarze, Per, Norwegian Institute of Public Health, Domain of Infection Control and Environmental Health, Department air and noise, per.schwarze@fhi.no,	2 SCIENTIFIC RATIONAL	 SCHEERFinalEng4.docx	Please see the answers (in red) within the file. Thank you for the positive comments and the support to the document.
17.	Martinez, Javier, JT International SA, 8 rue	2.1 Introduction	p.12, l.12-18 In describing what constitutes a "priority list additive" under the Directive, SCHEER excludes the text "and whether", and replaces this with a foreslash ("/"), to separate out the two limbs	The wording using the "/" is exactly what is included in the ToR coming from the Commission. The SCHEER is not in charge of changing it.

	Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other		of Article 6(2)(a). There is some ambiguity in the Directive in this regard, due to the wording and structure of Article 6. Article 6(1)(a) indicates that priority list additives will include those that have "one of the properties set out in points (a) to (d) of paragraph 2". However, since Article 6(2) is worded in terms of the testing to be performed by manufacturers, as opposed to identifying properties, it is unclear what constitutes "one of the properties" for the purposes of Article 6(1)(a). p.13, l.19-23 According to SCHEER, the precautionary principle "… stipulates that a reasonable suspicion of toxicity is sufficient to deny approval of such a substance..." and that "[t]he same reasoning applies to the addictive and attractive effects of tobacco additives..." Please remove this statement and also the following one as these are inconsistent with the TPD2, which does not allude to the puzzling notion that a "reasonable suspicion" should be the basis for decisions about the use of additives. On the contrary, Articles 6(2) and 7(9) require such decisions to be based on concrete evidence, i.e., findings that an additive increases the "addictiveness" of a product "to a significant or measurable degree." Notably, this is clearly known to the SCHEER as it is acknowledged in the 'background' (mandate) section on p.8, l.26, when referring to Article 7. The SCHEER conveys various references related to the "attractiveness" of additives recommending that this should also form part of any scientific assessment. We would like to underscore that: (i) "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which	 The sentence on the application of the PP has been re-phrased to avoid misinterpretations about risk management and inconsistencies with TPD. The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER

			Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. (ii) No scientific criteria have been developed to assess, and regulate on that basis, the "attractiveness" of tobacco products. Thus, JTI rejects the concept of "attractiveness" as a valid public policy objective for the regulation of tobacco product additives because of its inherently uncertain, subjective and arbitrary nature. It is inapplicable to propose a testing methodology framed around the subjective concept of whether an additive is "attractive". Moreover, JTI does not accept the intimation that a policy objective of additive regulation should be to render smoking less enjoyable. JTI does also manufacture cigarettes without additives to meet consumer's expectancies and preferences. Whether or not consumers prefer cigarettes with specific additives is largely a cultural matter, which varies between markets. Notably, cigarettes containing no additives are successful in some markets but not in others. If tobacco products with added additives were more "attractive" as inferred by SCHEER, then over time cigarettes with additives would come to dominate every market, which is simply not the case.	provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
18.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United	2.1 Introduction	Page 12, Lines 25-27 & Page 13, Lines 6-11, 24-33: No validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive.	For this reason, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). The SCHEER agrees that the text could be misinterpreted as

	Kingdom		Page 13, Lines 17-19: SCHEER's recommendation for manufacturers/importers to use the precautionary principle goes beyond the remit of Art. 6 of the Directive. It should be deleted as it is a preventative decision-taking approach to risk management. Pyrolysis is an artificial measure bearing with little relevance to consumer exposure as the test is devoid of tobacco. Page 13, Lines 11-12: Landmark reports on the risks of smoking were published by the Royal College of Physicians in the UK and the US Surgeon General in 1962 and 1964 respectively. Tobacco additives ensure consistency of the product across different tobacco crops, form a distinctive brand, and to enable consumers to distinguish brands across the market by establishing a typical taste and smell for the brand. Page 13, Lines 11-23: The health risks of smoking are well documented (Doll et al., 1976), and the reasons for smoking are varied. Data is available comparing smokers in markets where essentially no additives are added to cigarette (i.e. Virginia markets – including for example the United Kingdom, Canada and Australia) and those markets where additives are used in tobacco (i.e. American blend markets – including the USA and much of Europe apart from the UK and France). From the scientific data, there is no discernible difference in the epidemiological data particularly in the relative risks of cigarette smoking and diseases such as lung cancer and chronic	giving indication on risk management measures, which is not included in the SCHEER mandate. For this reason in the revised version, there is no reference to the PP but an advice is given to the assessor by the SCHEER on how to conduct the evaluation in case of uncertainties not solved by testing carried out following the step procedure. This could be due to the lack of validated studies for some end-points. See above the answer to similar comments. This is not considered a health benefit. The comparison between brands and the reasons for smoking among the population are issues outside the SCHEER ToR for this Opinion.

			obstructive pulmonary disease in countries where Virginia vs American blended products predominate (Lee et al., 2009). When comparing rates of cessation between markets with predominantly Virginia products vs those with a large majority of American blended products, quit rates appear to be slightly higher for American blend markets which is at odds with the belief that cigarette additives inhibit cessation. The authors conclude that this data indicates that there is no enhancing effect of additives on addiction and nor do they sustain smoking (Lee P , et al 2009; Sanders et al., 2012). Page 13, Lines 30-33: Pyrolysis of individual additives will lead to the formation of some small molecular weight compounds due to the analytical method, these will have CMR properties. However, these experiments have little relevance to what happens in a burning cigarette. We explore this topic in more depth in our response to Section 2.4.2. Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. Therefore, we recommend the use of comparative smoke chemistry and biological smoke testing of cigarettes both with and without additives in human relevant assays, and is most relevant to conditions of use and consumer exposure.	Please see the general answer to CT (answer n°1 to comment n°1). For CT please see the answer n°1 to comment n°1.
19.	Ureel, Ludwig, British American	2.1 Introduction	Opinion 2 seeks to advise the Commission "on the type and criteria for comprehensive studies…to assess the relevance of the individual	The SCHEER agrees that many of the additives used in the manufacturing of cigarettes are approved for use in the US by the Food and Drug Administration: they are on the list of ingredients

	Tobacco, ludwig_ureel @bat.com, United Kingdom		additives…interaction of the additive with other additives/ingredients is also considered" (p13:6-10) Whilst Opinion 2 sets out potential studies that could be used, it fails to consider their relevance to the use of additives in tobacco products. For example, assessing the local toxicity (such as eye irritation) of an additive used in a cigarette will arguably serve limited value in achieving the objectives set out in Article 6 TPD2. This is particularly so given that all of the ingredients on the Priority List have had a long history of use in other consumer goods, without any requirements for such comprehensive testing. The Opinion states that the precautionary principle should "come into full force" (p13:16-19). However, Article 6 and the terms of reference relate to the type and criteria for comprehensive studies required under TPD2. The precautionary principle appears to have no bearing on the type of studies to assess the relevance of additives. The Opinion makes an unsubstantiated assertion that "by making smoking more attractive, [additives] promote an extremely unhealthy behaviour" (p13:13-14), and adds that that "they will indirectly lead to adverse health consequences by increasing consumption of the product" (p13:21-23). SCHEER cites no evidence in support of this statement. If that were the case, a higher smoking prevalence should be observed in countries were	generally regarded as safe (GRAS) and/or are indicated as 'of no safety concern' by JECFA or EFSA when used at the actual levels of use in food; in many cases, they are also considered safe by FEMA (Flavour and Extracts Manufacturers Association). However, these evaluations apply to ingredients in foods or cosmetics that are ingested or topically applied. This exposure route differs significantly from the one typical for additives in tobacco, which are either transferred to inhaled smoke in pure form, or are combusted and converted via pyrolysis into potentially toxic products. Therefore the '*long history of use in other consumer goods'* is not synonymous of safe use in tobacco products. Referring to the specific case of eye irritation, whenever an eye irritant is formed after burning and is present in smoke, the potential for eye irritation exists. Anyway it should be noted that whenever there is a good scientifically based and acceptable reason for a derogation to present data for a specific end-point a justification can be provided (exactly as for any other regulatory requests). This is clarified in the revised version in the appropriate subchapter The sentence on the application of the PP has been re-phrased to avoid misinterpretations about risk management and inconsistencies with TPD. WHO, FDA, Health Canada would disagree based on a large body of literature. This is why the WHO-FCTC advises Parties of the FCTC to regulate, by prohibiting or restricting, ingredients that may be used to increase attractiveness.

			additives are commonly used vis-à-vis "Virginia markets" or countries where their use is heavily restricted. However, this is not the case.. Publicly available evidence demonstrates no link between additives and prevalence [70]. Moreover, consumers in "Virginia markets" would arguably find additives to be unattractive. When additive-free cigarettes were introduced as a variant to many traditional US blend style brands, the WHO found that, "cigarettes claimed to be without additives.. have never been demonstrated to be less dangerous or addictive than conventional cigarettes" [50]. Long term epidemiological studies demonstrate no obvious difference in the risks of cigarette smoking and diseases e.g. lung cancer and COPD, between smokers that have historically smoked cigarettes with no or few additives, and those that smoke cigarettes which include additives [49].	This is a different issue; the Opinion does not say that cigarettes without additives have been proven to be less harmful.
			All cigarettes, with or without additives, are addictive. The Opinion refers to the "addictive [and attractive] effects of tobacco additives..." This contradicts the 2010 SCENIHR Opinion [44], which failed to identify any ingredient which had an addictive effect, and concluded that there was no evidence that additives increase the addictive effect of nicotine. SCHEER has not cited, nor are we aware of, any additional information published since then which is likely to have altered this conclusion.	These statements are not contradictory, as the statement in the current Opinion describes how information on the addictive effect can be derived, whereas the 2010 SCENIHR statement is on the current state of knowledge on the addictive character of additives.
			SCHEER cites no evidence in support of its statement that tobacco additives "have no health or other benefits for the consumer" and "promote an extremely unhealthy behaviour." Whilst there are no health benefits of such additives there are other benefits such as malleability in the case of hand-rolling tobacco, quality and shelf-life. This is	The SCHEER adapted the sentence by removing 'or other'. Since the focus of the Opinion is related to health effects, the SCHEER agrees that the other 'benefits', as described in the comment, are not relevant and as a consequence 'or other' has been deleted.

			recognised in Canadian regulations which permit the use of additives essential to the manufacturing process –Health Canada exempted Glycerol and PG in the 2009 Bill C-32, an Act to amend the Tobacco Act, which aimed at removing flavours from products[60]. There are also important considerations regarding non-consumer benefits to be considered such as allowing consistency of tobacco sourcing as many of the additives iron out crop to crop variability in terms of taste and flavour in order to ensure a consistent return to farmers.	
20.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.1 Introduction	We suggest deleting the whole paragraph (p. 13, l. 11-23) "It should be noted that (…) by increasing consumption of the product". The recommendations on how to set the level of proof of safety and how to apply the precautionary principle in this paragraph are not within SCHEER's mandate and contradict Art. 6 and 7 TPD. As previously stated, SCHEER has been asked to advise on how to assess risks rather than how to manage them. SCHEER's mandate is to provide the Commission with scientific advice on the type of and criteria for the studies to be carried out under Art. 6 TPD, and not on how the use of additives in cigarettes and roll-your-own tobacco should be regulated. The precautionary principle is a risk management strategy for political decision-makers (EU Commission, Communication from the Commission on the precautionary principle, COM(2000)1, in the following: the "Communication"). The precautionary principle gives guidance on how to balance freedoms and rights of individuals, industry and organizations with the need to reduce or eliminate the risk of adverse effects to the environment or to health (Communication, p. 1). There is never a clear cut answer on how to balance these freedoms	The SCHEER disagrees: how to manage risk was not suggested. On the contrary the SCHEER gave as far as possible the type and criteria for comprehensive studies to be requested. The sentence on the application of the PP has been re-phrased to avoid misinterpretations about risk management and inconsistencies with TPD. The SCHEER also gave indication that in order to evaluate data for risk assessment a WoE approach should be used. Only when uncertainties cannot be reduced by comprehensive studies, the SCHEER advice that risk reduction measures should immediately be applied in accordance with the precautionary principle and Article 7 of the TPD. Some sentences have been rephrased to avoid misinterpretation.

			and risks "but a whole range of actions available to decision-makers under the head of the precautionary principle" (Communication under "5.2 Measures resulting from reliance on the precautionary principle"). The EU Commission explains in this regard: "Judging what is an 'acceptable' level of risk for society is an eminently political responsibility" (Communication, p. 4) and "[t]he appropriate response in a given situation is thus the result of an [sic] political decision, a function of the risk level that is 'acceptable' to the society on which the risk is imposed." While the precautionary principle plays a role when discussing how to deal with a risk (as DKFZ does), it has no relevance when the regulator has already taken this decision. In the latter case, the regulator's decisions on how to apply the precautionary principle should be respected (see section 2.4). In the case at hand, the EU legislator has already decided by adoption of the TPD how to apply the precautionary principle to address risks associated with additives in cigarettes and roll-your-own. Contrary to SCHEER's suggestion to ban all additives that are reasonably suspected of being toxic, addictive or attractive (p. 13, l. 19-23), the EU legislator has decided, through the TPD, to require manufacturers and importers to carry out studies to further examine certain additives. SCHEER suggests that "the level of proof of safety must be set much higher than for other products" (p. 13, l. 15-16), but the EU legislator has decided the level of proof by adoption of the TPD. According to Art. 7(9) TPD Member States shall ban tobacco products if they contain additives in quantities that "increase the toxic or addictive effect, or the CMR properties of a tobacco product at the stage of	The SCHEER agrees that the level of proof of safety is not indicated in the TPD. The text has been changed accordingly.

			consumption to a significant or measureable degree".	
21.	Thielen, Anja, Deutscher Zigarettenverband DZV, a.thielen@zigarettenverband.de, Germany	2.1 Introduction	*Repetition of comment Nr 11*	See answer to comment n°11.
22.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.1 Introduction	*Repetition of comment Nr 11*	See answer to comment n°11.
23.	Marshall, Lindsay, Humane Society International, lmarshall@hsi.org, United Kingdom	2.1 Introduction	Step 3 records the testing profile that may be required and includes in silico, in vitro and in vivo methods for assessing toxicity, CMR and addictiveness. We see no need to employ in vivo testing for the assessment of toxicity. We note that a reasonable suspicion of toxicity is enough to deny approval of a substance (Page 13, line 20) and we would infer that a reasonable suspicion of toxicity may be derived from pre-existing data or from an AOP mapping/chemical grouping approach and therefore should not require animals. We feel that testing additives for attractiveness is a wholly subjective, human quality and that this makes animal testing totally unacceptable, and not able to provide any data for the additives in question.	The use of animal testing for collecting new data of toxicity is not endorsed; the possibility to make a sound evaluation and to define if the additive acts via a specific AOP depends on the amount of available data as well as on the possibility to obtain new one by in silico and in vitro methods.
24.	Bosse, Andrea, DVAI	2.1	The Directive 2014/40/EU states that the additives should not increase the CMR properties of the	Since art. 6(2) of the TPD says in bullet point (a): (a) **contributes to the toxicity or addictiveness of the**

	- German Association of the Flavour Industry, info@dvai-dvrh.eu, Germany	Introduction	product [1]. The wording and the objectives in this opinion differ [2] from the Directive and lead to the misinterpretation "that additives which produce substances with CMR-properties will not meet the TPD requirement"[3] . The wording of the report should be adapted to ensure that the objective of the reports corresponds with the objective of the directive. [1] Directive 2014/40/EU, Article 6, 2. d) "leads to the formation of substances that have CMR properties, the quantities thereof, and whether this has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree." Directive 2014/40/EU, Article 7, 9. "Member States shall, on the basis of scientific evidence, prohibit the placing on the market of tobacco products containing additives in quantities that increase the toxic or addictive effect or the CMR properties of a tobacco product at the stage of consumption to a significant or measureable degree." [2] SCHEER: 1.2 Terms of reference, Opinion 1 page 10; SCHEER: 2.1 Introduction page 12; SCHEER: 2.4.1.2 Evaluation, page 20: d) "Leading to the formation of substances that have CMR properties / increasing the CMR properties in any of the products concerned (cigarettes/roll-your-own) to a significant or measurable degree. [3] SCHEER: 2.4.2.3. Evaluation page 23: …For instance, if it is demonstrated that compounds proven to have CMR properties are generated from pyrolysis of an additive, this additive will not meet	**products concerned**, and whether this has the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree; and considering the SCHEER approach to comply with the evaluation of the contribution to the overall toxicity, the objectives seems to be the same. However, to avoid misinterpretation the wording in the appropriate paragraphs has been changed.

			the TPD requirement."	
25.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.2 Knowledge gaps identified in Opinion 1	The Opinion states that "[T]here was generally scant toxicological information regarding tobacco additives analysed for Opinion 1" (p.14:2-3). Whilst we acknowledge that there may be limited information available on the toxicity of additives per se, comparable situations exist in other industries. This was acknowledged by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), which states that "it is neither possible nor necessary to conduct toxicological studies on all individual flavouring substances used in food. The majority of flavouring substances are members of groups of substances with common metabolic path-ways, and typically, individual members of such a group display a similar toxicity profile. " [16]. It was for this reason that JECFA introduced a "Procedure for the Safety Evaluation of Flavouring Agents" which does not mandate a full risk assessment of individual additives if no toxicological data exists, but instead recommends the assessment of groups of structurally related flavour compounds. Similarly, the EU REACH regulations do not require toxicological studies for specific toxicological end-points on individual additives, but instead use safety factors to extrapolate findings. For example, a short term feeding study is used to determine a Derived No Effect Level and deemed to be safe in chronic inhalation exposure [55]. This is a common practice as known as "read across" and as such is aligned with the requirements for replacement, refinement	The issue of grouping or application of read across is detailed in the preliminary Opinion in paragraph 3.4 (in the general description of the step procedure (page 17, line 5-12): *This procedure could be applied to single individual additives; if necessary* ***additives could be grouped****, following rules previously established in other fora to evaluate e.g.* ***groups of food flavouring at EFSA***[1] *or* ***groups of chemicals in Regulation (EC) No 1907/2006*** *i.e. REACH (to apply the read-across principles)*[2] *in order to limit the use of animal testing (as requested in art. 13). The ECHA provides practical guidance on the issue (available at the above-mentioned website link); however, to this aim, the approach described in the OECD GUIDANCE ON GROUPING OF CHEMICALS No. 194*[3] *is recommended.* The SCHEER refers to EFSA procedure to evaluate flavouring substance in food, not to the similar approach followed by JECFA, simply because it is used under the umbrella of EU Regulation. The same applies to the REACH regulation. Therefore there is no disagreement between the commenter and the preliminary Opinion.

[1] https://www.efsa.europa.eu/en/topics/topic/flavourings

[2] http://echa.europa.eu/support/grouping-of-substances-and-read-across

[3] GUIDANCE ON GROUPING OF CHEMICALS, SECOND EDITION Series on Testing & Assessment No. 194 (2014) available at http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2014)4&doclanguage=en

			and reduction of the use of animals for toxicological testing. Notwithstanding this, currently available scientific evidence indicates that the levels of additives used in the production of tobacco products sold in the EU and elsewhere, do not increase the toxicological risk associated with the use of tobacco products, nor do they enhance the pharmacological effects of nicotine. The Opinion claims that there is little data available on the effects of additives in tobacco following inhalation (p.14:6-7) [9]. However, as stated in our response to Opinion 1, the tobacco industry has published a large amount of peer reviewed literature on the additives it uses, and the results of test data generated on those additives under conditions of use, both singly and in combination. Studies by BAT [1], [2], [3] report the findings of studies in which mixtures of additives were tested. In these studies, additives were added to tobacco at levels representative of those used in BAT commercial products. The results are consistent with other extensive data sets from the industry which are also available in the public domain. The Opinion states that "In the tobacco matrix, either the intact additive or its pyrolysis products may react with other additives, tobacco- or smoke components (pyrosynthesis)." (p.14:22-24) This, together with the requirement under A6 to take into account the intended use, further validates the use of comparative testing, as comparative testing will	**The SCHEER disagrees** with the statement " *the levels of additives used in the production of tobacco products sold in the EU and elsewhere, do not increase the toxicological risk associated with the use of tobacco products"*, meaning that additives are present at such low levels compared to the tobacco matrix that their influence on the toxicity, addictiveness or CMR properties is insignificant because it is the high toxic potential of the tobacco matrix that makes it experimentally problematic to study the influence of a single additive on the toxicity, addictiveness or CMR properties of the matrix, and not so much the low quantity of additives present in the matrix. The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. Please see the answer to comment n°1 for a comprehensive explanation about the SCHEER reasoning on CT.

			include reactions that are relevant at the stage of consumption. The Opinion states that "[a]lthough for most tobacco additives, direct information about their possible contribution to addictiveness and characterising flavours does not exist, information can be derived from the mode of action of the additive" (p.14:28-30). This contradicts the conclusions of the 2010 SCENIHR Opinion on Addictiveness and Attractiveness of Additives, which failed to identify any ingredient which had an "addictive" effect, and concluded that there was no evidence that additives increase the "addictive" effect of nicotine [44]. SCHEER has not cited, nor are we aware of, any additional information published since then which is likely to have altered this conclusion.	These statements are not contradictory, as the statement in the current Opinion describes how information on the addictive effect can be derived, whereas the 2010 SCENIHR statement is on the current state of knowledge on the addictive character of additives.
26.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.2 Knowledge gaps identified in Opinion 1	p. 14, l. 6-7 SCHEER's statement referring to "Data on the effects of additives in tobacco following inhalation is generally not available" is incorrect. Data from 90-day inhalation studies were provided for the majority of additives. (Gaworski et al., 1998, Carmines et al., & Vanscheeuwijck et al., 2002; Baker et al., 2004a-c, Renne et al., 2006, Coggins et al., 2011a-i; Gaworski et al., 2011) p.14, l.22-24 Please consider that the additive and/or its pyrolysis products will interact with other additives, smoke components and tobacco. As a result, it is counterintuitive to study an additive in isolation as it is not possible to assess any synergistic and/or antagonist effects. As individual chemicals, the constituents of tobacco smoke coming from pyrolysis of tobacco and of added additives are known to have numerous chemically and biologically significant effects, but the relevance of these constituents, originating from additives to the overall toxicity of cigarette smoke itself is not	The SCHEER is here referring to the general situation, not exclusively to the 15 additives in the priority list. The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, also in view of the SCHEER indication about CT. Please see the answer to comment n°1 for a comprehensive explanation about the SCHEER scientific position on CT. The SCHEER can agree with the comments that reactions among tobacco products components as well as the possible interaction leading to more-than-additive effects will not be identified by testing the single additive/ingredient. On the other hand, CT at the moment could hardly provide the appropriate sensitivity to see any differences. Therefore the SCHEER approach is the only

			known. p.14, l.28-32 SCHEER precisely concedes that direct information about the possible contribution of additives to "addictiveness" does not exist. Thus, the obscure notion recounting that "information can be derived from the mode of action of the additive" is thus hard to fathom. No scientific human study provides a so-called mode of action of a single additive, via increased nicotine bioavailability or local anesthetic effects, with respect to smoking behavior or "addictiveness." p. 14 l.28-32 and p.15. l. 8-9 The SCHEER seemingly uses the terms mechanism of action and mode of action interchangeably. For example, the SCHEER contends that "the [addictiveness] assessment can be guided by the knowledge of the mechanism of action." Nonetheless, the knowledge of the mechanism(s) of action related to the dependence potential of a given additive added to cigarettes is not established nor documented. Mechanism of action has been defined as "a complete and detailed understanding of each and every step in the sequence of events that leads to a toxic outcome." (ECETOC, 2007), which includes detailed knowledge of the causal and temporal relationships among all the steps leading to a specific effect. Accordingly, the EPA 2009 noted that the "[m]echanism of action represents a more detailed understanding and description of events than is meant by mode of action."	pragmatic way to comply with the requests (see the answer to comment n.1, referring to how to deal with mixture toxicity). This is why the SCHEER proposes a step-wise approach: Experimental testing of the dependence potential of tobacco additives is still limited due to the lack of validated administration models for the examined individual compound itself and in co-administration with other tobacco additives. In the proposed step-wise approach, the SCHEER discusses the possibilities to experimentally quantify the dependence potential of tobacco additives (often) co-administered with nicotine. The SCHEER agrees with the comments. The text has been changed accordingly.
27.	Simms, Liam, Imperial Tobacco Limiuted, liam.simms@	2.2 Knowledge gaps identified in	Page 14, Lines 6-7: There are various studies in the scientific literature which assess the effects of additives in tobacco following inhalation in animals (Baker, et al.,	The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, also in view of the SCHEER

	uk.imptob.com, United Kingdom	Opinion 1	(2004), Carmines et al., (2002), Gaworski et al., (1998), Gaworski et al., (2011) and Renne et al., (2006). Klus et al., (2012) reviewed the influence of additives on cigarette related health risks. Ultimately they concluded "…tobacco additives have only occasional and limited effects on cigarette mainstream smoke composition, which are almost never reflected in toxicological in vitro assays or in vivo studies, and do not confirm the assumption that the additives used in cigarette manufacturing increase the risk of smokers for any cancers, chronic obstructive lung disease or cardiovascular diseases". Page 14, Lines 12-17: No validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. The potential for an additive to transfer intact into the mainstream smoke from the tobacco matrix may be predicted from its volatility, and thermal stability. During use of a combusted tobacco product, volatile additives distil from the tobacco column and transfer intact into the mainstream smoke (Baker and Bishop, 2004). The peer-reviewed literature demonstrates that a representative selection of volatile additives transferred largely intact into mainstream smoke from the tobacco matrix (Green et al., 1989, Purkis et al., 2011). Non-Volatile additives will not distil from the tobacco column and will either be completely combusted or undergo pyrolysis (endothermic	indication about CT. For this reason, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Furthermore, please refer to our general statement on comparative testing (answer n°1 to comment n°1).

			decomposition of organic compounds and material) (Baker and Bishop, 2005). These pyrolysis products are not expected to significantly change the quantity or nature of the mainstream smoke generated through the combustion of the tobacco matrix (Purkis et al., 2011). Art. 6.3 of the Directive states "….studies shall take into account the intended use of the products….". This hypothesis is not representative under the conditions required for the intended use of tobacco products and therefore falls short of the mandate. In contrast, Imperial Tobacco Ltd assesses the appropriateness and acceptability of each and every one of the additives we use. We employ a panel of experienced toxicologists to carry out risk assessments on additives and to judge the suitability of these additives for inclusion in our products. A risk assessment of an additive added to a tobacco product, cannot solely rely on data generated from smoke chemistry and biological testing of the additive in situ. Risk assessments are also carried on the single additive. Firstly, human exposure is calculated (using smoke transfer studies and upper bound consumption levels) and a risk assessment on the single additive is carried out based on that exposure. This approach is used in combination with smoke chemistry and associated biological data of the additive when combusted in a cigarette, to indicate whether or not an additive will contribute to the toxicity of the product. Page 14, Lines 33-34: We disagree with this statement. In addition to the hazard and exposure data available in the published literature, we generate our own data to inform our	The SCHEER indicate that the test outcomes should be relevant for tobacco smoking, meaning that, e.g. for toxicity testing the inhalation route is much more relevant than the oral one or that, whenever a pyrolysis study is carried out, the temperature and other experimental conditions should the one typical of smoking. Since data are already available and carried out by a Panel of experienced toxicologist this should facilitate TI in complying with the step procedure. The SCHEER refers to the situation encountered by SCENIHR during the preparation of the previous Opinion (as stated in the title of the subchapter). This has been clarified.

			risk assessment process. Internally, generated biological and chemical data has been submitted to the European Member States in compliance with EUTPD 2001/37.	
28.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.2 Knowledge gaps identified in Opinion 1	SCHEER is relying on SCENIHR's analysis of "major data gaps already identified in Tobacco Opinion 1 for the 15 additives" (see, e.g., Abstract at p. 5, l. 5). We disagree with some of SCENIHR's analysis and refer in this respect to our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", in which we stated (comment to the Abstract): "Had the Committee carried out a comprehensive review of all the evidence, it would have realized that most of the "gaps" it identified are in fact not gaps in the current state of science but in its literature research. Prior to requesting additional testing from manufacturers, it is essential to have completely assessed existing data and evidence. In particular, SCENIHR would have realized that, contrary to its statements, inhalation toxicity data (p. 4, l. 43), data on pyrolysis and exposure to combustion reactions products (p. 4, l. 45) and data on mixture toxicity (p.5, l. 2) are not "scarce" or "negligible" but have been reported in peer reviewed publications not yet considered by SCENIHR, which we upload in the corresponding sections." We have not changed our views in this respect and we therefore suggest to remove the sentence "Generally speaking (…) if not impossible" (p. 14, l. 33-34). We consider that these studies use the best currently available methods.	Please see the answer given to the same comment received for Opinion 1. In Opinion 1 SCENIHR was not asked to carry out a risk assessment but a prioritization based on hazard of a large number of additives. Opinion 1 served, as stipulated in the methodology, to the compilation of a priority list. This list will assist, in line with Article 6 of Directive 2014/40/EU, the Commission to develop priority list of at least 15 additives for which enhanced reporting obligations will apply (as described in the section 1 'background'). The SCHEER agrees that '*Prior to requesting additional testing from manufacturers, it is essential to have completely assessed existing data and evidence'.* This is exactly the philosophy behind the proposed step procedure, according to which all the data available to TI is retrieved and presented: in case the information is sufficient to a sound assessment of the additive safety, no need for further testing (Step 3) is necessary. Therefore there is no disagreement between the commenter and the SCHEER. The SCHEER view does not change either. However, the wording has been modified for better clarity.

			However, we agree that some knowledge gaps still exist. As already stated, we encourage SCHEER to trigger the development of relevant research, in line with the Committee's expressed interest at p. 69, l. 25-26 ("It is advised that independent bodies or organisations begin conducting relevant research").We would welcome any opportunity to contribute to this research and method development. In the meantime, we will carry out and report on studies using the best currently available methods.	Reporting on research needs was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted. A paragraph is added at the end of Chapter 4.
29.	Thielen, Anja, Deutscher Zigarettenverband DZV, a.thielen@zigarettenverband.de, Germany	2.2 Knowledge gaps identified in Opinion 1	Available and relevant information and data were not considered in the report of SCHEER. In chapter 2.2, SCHEER refers to the "general scarcity of information" regarding the toxicity of additives. However, much of the available relevant information and data were not considered in the SCHEER report. For decades' scientists including those from within the tobacco industry, have been investigating the effects of tobacco additives on the composition and the toxicity of tobacco smoke. Much of this data have been published in peer reviewed journals . However, many of these studies have been ignored in the SCHEER preliminary opinion which undermines its relevance - just as they were not being considered in the report of SCENIHR, 2010 either. All available and relevant information should be considered and discussed by an independent scientific committee assigned to give a recommendation for a testing strategy. Carmines EL: Evaluation of the potential effects of ingredients added to Cigarettes — Part 1: Cigarette design, testing approach, and review of results, in Food and Chemical Toxicology, 2002, 40(1):77-91; Rodgman, A.: Some Studies of the Effects of	The SCHEER refers to the situation encountered by SCENIHR during the preparation of the previous Opinion (as stated in the title of the subchapter). This has been clarified. However, if the commenter refers to CT, please see the SCHEER approach on this kind of studies by reading the answer to comment n°1. The philosophy behind the proposed step procedure is that all the data available to TI is retrieved and presented to the MS: in case the information is sufficient to a sound assessment of the additive safety, no need for further testing (Step 3) is necessary. It is not the SCHEER that have to evaluate the available information: this is the task of assessor at the MS level. The proposed step procedure is a general framework for additive safety evaluation. The availability of data should facilitate TI in complying with it.

			Additives on Cigarette Mainstream Smoke Properties. I. Flavorants; Beiträge zur Tabakforschung International; 20, 2002. 83 - 103. Rodgman, A.: Some Studies of the Effects of Additives on Cigarette Mainstream Smoke Properties. II. Casing Materials and Humectants; Beiträge zur Tabakforschung International; 20, 2002. 279 - 299. Baker RR, Massey ED, Smith C, An overview of the effects of tobacco ingredients on smoke chemistry and toxicity, in Food Chem. Toxicol. 2004a; 42 Suppl. S53-83. Coggins, C. R., Wagner, K. A., Werley, M. S., and Oldham, M. J.: A comprehensive evaluation of the toxicology of cigarette ingredients: carbohydrates and natural products; Inhal.Toxicol.; 19-4-2011.	
30.	Thielen, Anja , Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.2 Knowledge gaps identified in Opinion 1	*Repetition with comment 29*	Please see the answer to Comment n°29.
31.	Bosse, Andrea, DVAI - German Association of the Flavour Industry, info@dvai-dvrh.eu, Germany	2.2 Knowledge gaps identified in Opinion 1	The SCHEER opinion does not include all available data. In this context it should particularly be emphasized that the report of the German standardization organization DIN SPEC 10133 [1] giving recommendations for the toxicity testing strategy of tobacco additives is not mentioned. [1] Deutsches Institut für Normung DIN: DIN SPEC 10133: Toxicological assessment of additives for	The document referred to is in essence a comparative testing approach. Please refer to our general answer on comparative testing (answer n°1 to comment n°1).

			tobacco products – A guidance, 2004, Beuth Verlag.	
32.	Vizée, Huub, delfortgroup, huub.vizee@delfortgroup.com, Austria	2.3 Methodology	Attractiveness In Opinion II next to addictiveness and toxicity SCHEER regularly states that additives will also be judged on their attractiveness. However; nowhere in the mandate attractiveness is requested to be looked at. The mandate for SCHEER clearly states: "Based on scientific evidence (including a review of relevant scientific data) and other relevant information currently available (initial indications, regulation in other jurisdictions), the Committee is asked to identify - for each category separately - those additives that fall/are suspected to fall within the scope of the following categories: a. Contribution to the toxicity or addictiveness of the products concerned / increases the toxicity or addictiveness of any of the products concerned to a significant or measurable degree; b. Resulting in a characterising flavour; c. Facilitating inhalation or nicotine uptake; d. Leading to the formation of substances that have CMR properties / increasing the CMR properties in any of the products concerned (cigarettes/RYO) to a significant or measurable degree" Attractiveness therefor cannot and should not be used by SCHEER to judge an additive	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
33.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United	2.3 Methodology	SCHEER states that additives have no "benefits for the consumer", and that they "promote an extremely risky behaviour". Whilst we accept that there are certainly no health benefits in the use of these additives, a number of the priority additives have clear functional benefits including the preservation of shelf-life, and humectants for example are essential in fine-cut tobacco as they	Since the focus of the Opinion is related to health effects, the SCHEER agrees that the other 'benefits', as described in the comment, are not relevant and as a consequence 'or other' has been deleted.

	Kingdom		allow the physical rolling of the product without fragmentation of the tobacco. This fact has been recognised in the Canadian 2009 Bill C-32 [60], an Act to amend the Tobacco Act, which was aimed at removing flavours from products and which permits only the use of additives essential to the manufacturing process – this allows the continued use of humectants such as glycerol and propylene glycol.	
34.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.3 Methodology	While a regulatory framework should be developed to assess additives-related toxicity for use in tobacco products, the development of adequate test methods should be based on objective scientific standards, using existing toxicological testing standards and assays recognized by bodies such as the OECD, WHO and the German Standardization Organization DIN. In the absence of a regulatory framework regarding the assessment of ingredients, JTI has developed internal procedures for the evaluation of ingredients: it has a product stewardship program in place to conduct a toxicological risk assessment as well as a battery of well-recognized chemical and toxicological tests. JTI ensures, through these tests, that ingredients do not increase the inherent toxicity of tobacco products. An ingredient may be added to a tobacco product if it does not increase the toxicological properties compared to a tobacco product without this ingredient ("no change approach"). Two very important factors in the assessment and evaluation of an ingredient are (i) a hazard identification for the ingredient based upon its known toxicological properties and (ii) an exposure assessment that estimates maximal potential daily exposure using conservative assumptions. The initial hazard identification is used to evaluate the toxicological properties of an ingredient. JTI	There is no disagreement. The SCHEER has indeed asked to use, whenever possible, existing toxicological testing standards and assays recognised by bodies such as the OECD. The SCHEER welcomes the fact that TI already has a number of studies ready for submission on the additive itself. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, also in view of the SCHEER indication about CT. The availability of data should facilitate JTI in complying with the step procedure proposed by the SCHEER.

			rejects the use of any ingredient identified by regulatory or expert authorities as a carcinogen, reproductive/developmental toxicant, genotoxicant or human respiratory allergen. If an ingredient's regulatory status or safety assessment as a neat ingredient provides insufficient information to support its use under intended usage conditions, then JTI will conduct additional chemistry and/or toxicology studies. These studies are used to evaluate and assess potential ingredients, providing a framework for decision-making using a tiered investigational approach. These tests may include: (a) testing of individual materials; (b) pyrolysis and/or smoke transfer testing; (c) a quantitative analysis of smoke constituents, comparing cigarettes that contain the relevant ingredients to cigarettes that do not contain the relevant ingredients; (d) in vitro genotoxicity assays of cigarette smoke condensate; (e) in vitro cytotoxicity assays of cigarette smoke condensate; (f) sub-chronic 90-day rodent inhalation studies; and (g) mouse dermal application carcinogenesis studies. JTI ensures, through these tests, that ingredients do not increase the inherent toxicity of tobacco products.	
35.	Krupitsky, Evgeny, St.-Petersburg Bekhterev Research Psychoneurological Institute,	2.3.1 Development of the general approach to assess the effects of tobacco	It might be problematic to extrapolate results of in vitro studies of addictive potential of tobacco additives on the human subjects. I believe the separate studies in humans are necessary and important.	The SCHEER agrees that the IVIVE could be difficult, but deemed it unethical to ask for animal studies in this area. Human studies are discouraged but still allowed, and specific cases are already described in the preliminary Opinion (e.g. testing for characterising flavour).

	kruenator@gmail.com, Other	additives		
36.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.3.1 Development of the general approach to assess the effects of tobacco additives	The concept of "addictiveness" needs to be (i) adequately defined and (ii) objectively measureable before it may be considered as a basis for regulation. Meanwhile, the "addictiveness" definition provided in the TPD2 guidelines fails to account for the multiple reasons (other than the pharmacological aspects of tobacco) contributing to why people choose to smoke. JTI does also manufacture cigarettes without additives to meet consumer's expectancies and preferences. Whether or not consumers prefer cigarettes with specific additives is largely a cultural matter, which varies between markets. Notably, cigarettes containing no additives are successful in some markets but not in others. Nevertheless, adult consumers are entitled to accurate and non-misleading information, therefore it is essential to point out that while smoking cigarettes, with or without additives, can be "addictive", no tobacco constituent or additive, or a mixture of additives, including those mentioned in the priority list, precludes a motivated smoker from successfully quitting smoking. Smokers can stop smoking. This applies equally to cigarettes with or without additives. Accordingly, the study by Sanders et al. 2012 concluded that "the presence of ingredients currently being added to tobacco does not increase inherent cigarette addictiveness." This is echoed by the steady decline of smoking in Western countries in the recent decades. For example, the prevalence of current cigarette smoking among U.S. adults declined from 24.7 % in 1997 to 15.1 % in 2015. Moreover, according to two large studies (Sarna et al. 2008; Lopez-Quintero et al. 2011) conducted in the U.S.,	While the SCHEER agrees that that there are multiple reasons for tobacco addiction, the current Opinion is on the contribution of additives to addictiveness.

			approximately 80 % of smokers definitively quit smoking during their lives, irrespective of the presence of additives.	
			6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion. A scientifically valid and convincing approach to evaluating the dependence potential of a given additive is not available up to now. Tellingly, the SCHEER repetitively mentions that "no addictiveness and attractiveness tests are available" see e.g., p.68, l. 22-23; p. 4, l. 23-33; p. 66, l. 32-33. Absent of concrete and validated proposed methods regarding to the 'addictiveness" of individual additives, it is unrealistic to provide a science-based regulatory response. Finally, as researchers from the Gillings School of Global Public Health, University of North Carolina, pointed out in 2014, "[m]ost of the harms from smoking come from tobacco constituents that are naturally present in tobacco (Hecht, 2012)…. health communication efforts might be more effective if they emphasize that all cigarettes—even so-called "natural" and "additive-free" cigarettes—are irrevocably dangerous because they contain harmful components." (Hall et al. 2014)	The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Whether or not most of the harm results from natural tobacco components is irrelevant here, as the current Opinion is on the contribution of additives to toxicity and addictiveness.
			p. 14, l. 43 SCHEER proposes a "tiered" evaluation system, suggested by the German Cancer Research Center. Please mention that this "tiered" entails several decision points, each of which would result in rejection of the additives if the data were not favorable and prevent further testing. p. 15 l.8-9 Contrary to SCHEER's assertion, the	The SCHEER step procedure took inspiration from the German Cancer Research Centre, but then it developed its own proposal. The safety assessment will not necessarily lead to rejection: it depends on the data available, exactly as for any other chemicals. The text has been adapted to include the suggestion. The term 'available' has been added to 'knowledge' to address the comment.

			mechanisms underlying "addictiveness" of the final tobacco product are not elucidated.	
37.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.3.1 Development of the general approach to assess the effects of tobacco additives	Page 15, Lines 2-8: If in silico data or read-across data produces an in silico alert for CMR, a weight of evidence approach should be used, i.e. comparing different studies, for example, in vitro and any animal testing data if it is available, to determine whether an additive has CMR properties or not. An in silico alert for CMR alone is not sufficient to determine a CMR, due to the relative high false-positive predictions of in silico techniques (Serafimova et al., 2010) Page 15, Lines 8-9: No-validated tests for addictiveness exist. The SCENIHR report of 2010 concluded that current methods are not adequate for a reliable quantification of attractiveness or addictiveness of nicotine and tobacco additives. There are no validated studies of any kind on attractiveness which would substantiate SCHEER's call for an attractiveness assessment. Furthermore, attractiveness does not fall within SCHEER's Mandate for this Preliminary Opinion 2. All methods that inform regulatory measures must be robust, reproducible, and repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology. We recommend that SCHEER only request data generated from test methods which have undergone method validation. The OECD (2005) defines method validation as "…a process based on scientifically sound principles by which the reliability and relevance of a particular test, approach,	There is no disagreement between the commenter and the SCHEER. This paragraph is only a very brief description of the procedure: all the steps are described in the details in the following sessions with exactly the approach proposed in the comment. The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterizing flavours. At other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". The SCHEER has indeed asked to use whenever possible existing

			method or process are established for a specific purpose". Test methods which have not been validated, nor gained international regulatory acceptance could give misleading results as the reliability and relevance of the method has not been established (Hartung et al., 2004). Consequently, it is unscientific to use assays lacking proper validation.	toxicological testing standards and assays recognised by bodies such as the OECD. Unfortunately for some end-points, methods alternative to animal testing is not yet available: in this respect the situation can be similar to the one experienced in the cosmetic area. The SCHEER agrees that validated methods should be the best choice; this is the reason why the SCHEER has pointed out the areas in which such validated tests are not available.
38.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.3.1 Development of the general approach to assess the effects of tobacco additives	As noted in our comment to section 2.1, political considerations on how to apply the precautionary principle go beyond SCHEER's mandate. Therefore, we suggest that in this section the sentence "Given the fact (…) not appropriate" (p. 14, l. 38-40) should also be deleted. As further explained in our comment to the Abstract, DKFZ's proposal is not in line with Art. 6(2), (3) and Art. 7(9) TPD. These provisions of the TPD require a weight of evidence approach so that, in case any concern arises in step 2 regarding toxicity, addictiveness and CMR properties, testing should proceed to step 3, including comparative testing. We therefore suggest that the phrase "is the most pragmatic (…) testing" (p. 14, l.41-p.15, l. 2) should be replaced by "favorable for the assessment of the toxic and addictive effects of additives in cigarettes and roll-your-own tobacco and whether, and at which level, they may result in a characterizing flavor. After completion of all three steps, the evidence obtained in all three steps should be assessed and weighted (weight of evidence approach)." At the same time the reference to "attractive effects" would be replaced with a reference to characterizing flavor, consistent with Art. 6(2) and 7(1) TPD. We further suggest inserting after "next," (p. 15, l.	There is indeed no reference to PP in the section 3.3.1. However, whenever relevant, the sentence on the application of the PP has been re-phrased to avoid misinterpretations about risk management and inconsistencies with TPD. The SCHEER step procedure took inspiration from the German Cancer Research Centre, but then it developed its own proposal. In case the comments refers to the SCHEER statement not to considered CT carried with currently available methodologies suitable to discriminate between tobacco product toxicity with and without an additive please see answer to comment n°1. The application of a WoE was already present in the preliminary Opinion (page 19 in section 3.4.1.1 Collection of literature data). The SCHEER advised to provide any available data. This means that TI can provide also the comparative testing studies if carried out before this Opinion was adopted. The SCHEER meant that no new animal studies should be conducted, but any data that are already available should be included in the dossier and analysed. It will be then the task of the assessor to give the right weight to any study (including CT) in a WoE approach. In case available data allow a proper evaluation, there is no need to go for further testing. Therefore there is no disagreement between the SCHEER and TI. This paragraph is only a very brief description of the procedure:

			3) "this evaluation is extended to the additive's pyrolysis products; if no data are available on the identity of the pyrolysis products, they need to be generated using relevant test conditions. In Step 3" and, after "followed by" "a testing battery including smoke chemistry and" to ensure consistency with other parts of the opinion 2, in particular the Abstract.	all the steps are described in the details in the following sessions with exactly the approach proposed in the comment. However, some more details have been added for clarity.
39.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.3.2 Addressing the major data gaps identified in Opinion I for the priority list additives	SCHEER is relying on SCENIHR's analysis of "major data gaps already identified in Tobacco Opinion 1 for the 15 additives" (see, e.g., Abstract at p. 5, l. 5). We disagree with some of SCENIHR's analysis and refer in this respect to our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", in which we stated (comment to the Abstract): "Had the Committee carried out a comprehensive review of all the evidence, it would have realized that most of the "gaps" it identified are in fact not gaps in the current state of science but in its literature research. Prior to requesting additional testing from manufacturers, it is essential to have completely assessed existing data and evidence. In particular, SCENIHR would have realized that, contrary to its statements, inhalation toxicity data (p.4, l.43), data on pyrolysis and exposure to combustion reactions products (p.4, l.45) and data on mixture toxicity (P.5, l.2) are not "scarce" or "negligible" but have been reported in peer reviewed publications not yet considered by SCENIHR, which we upload in the corresponding sections." We have not changed our views in this respect and we therefore suggest the word "major" in the title and in the text be deleted (Page 15, Line 10 - 12).	The SCHEER is here referring to the general situation, not exclusively to the 15 additives in the priority list. Please see the answer to comment n°1 for a comprehensive explanation about the SCHEER scientific position on CT. The SCHEER agrees that '*Prior to requesting additional testing from manufacturers, it is essential to have completely assessed existing data and evidence'.* This is exactly the philosophy behind the proposed step procedure, according to which all the data available to TI is retrieved and presented: in case the information is sufficient to a sound assessment of the additive safety, no need for further testing (Step 3) is necessary. Therefore there is no disagreement between the commenter and the SCHEER. The SCHEER view does not change either. However, in order to clarify, the wording has been modified.

			However, we agree that some knowledge gaps still exist and, as already stated, we encourage SCHEER to trigger the development of relevant research, in line with the Committee's expressed interest at p. 69, l. 25-26 ("It is advised that independent bodies or organisations begin conducting relevant research"). We would welcome any opportunity to contribute to this research and method development. In the meantime, we will carry out and report on studies using the best currently available methods.	Reporting on research need was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted. A paragraph has been added at the end of Chapter 4.
40.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.3.4 Information evaluation	SCHEER states that tests identified for the additives on the Priority List should be appropriate for the assessment of the toxic effects of tobacco additives, at the consumption stage. Accordingly, the relevance of having to carry out general local toxicity studies (p.29) on an additive used in a cigarette is highly questionable. Additionally to ensure appropriateness of the tests – we would reasonably expect only validated tests to be cited-particularly given that the window for testing and reporting does not allow for validation of a particular test methodology. The objective of the tests required under Article 6 TPD2 is to determine whether an additive impacts, inter alia, the toxicity "in any of the products concerned to a significant or measurable degree". Accordingly, it is reasonable to expect that the test articles should be tobacco products which contain the additives, and that they should be compared to control products which are additive free. We refer to our comments to Section 2 concerning SCHEER's reference to the alleged attractiveness of	The Chapter 3.3.4 Information evaluation refers to the methodology used by the SCHEER to draft the Opinion, not to the evaluation of the additives. The SCHEER has indeed asked to use whenever possible existing toxicological testing standards and assays recognized by bodies such as the OECD. Unfortunately for some end-points methods alternative to animal testing is not yet available: in this respect the situation can be similar to the one experienced in the cosmetic area. The SCHEER agrees that validated methods should be the best choice; this is the reason why the SCHEER has pointed out the areas in which such validated tests are not available. Regarding local toxicity testing, it should be noted that whenever there is a good scientifically based and acceptable reason for a derogation to present data for a specific end-point a justification can be provided (exactly as for any other regulatory requests). This is clarified in the revised version in the appropriate subchapter. For CT, please refer to answer n°1 to comment n°1. Please refer to our previous answer on the topic.

			additives.	
41.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.3.4 Information evaluation	SCHEER's in their opinion repeatedly state that "additives have the potential to directly or indirectly increase the toxicity of tobacco products." On the contrary, the scientific evidence substantiates the notion that the use of cigarettes additives at levels currently found in commercial brands does not appear to increase the overall toxicity of cigarettes, despite the SCHEER's oblivious reference to a series of scientific articles published in a 2011 special issue of Inhalation Toxicology. These studies support the 2002 and 2004 earlier findings from toxicity studies conducted by tobacco companies. Overall, the results of these studies, indicate that tobacco additives, even at exaggerated inclusion levels relative to commercial-use, produce minimal changes in the overall toxicity profile of mainstream cigarette smoke. Moreover, risk assessment strategies, i.e., effectiveness of harm reduction strategies, are not relevant in the context of additives-related toxicology, simply because cigarettes without additives are not less harmful. Notably, according to the World Health Organization (WHO), "cigarettes claimed to be without additives and made of 'organic' tobacco have never been demonstrated to be less dangerous or addictive than conventional cigarettes [with additives]." Accordingly, researchers from the Gillings School of Global Public Health, University of North Carolina, Chapel Hill, pointed out in 2014 that, "[m]ost of the harms from smoking come from tobacco constituents that are naturally present in tobacco (Hecht, 2012)…. health communication efforts might be more effective if they emphasize that all cigarettes—even so-called "natural" and "additive-free" cigarettes—are irrevocably dangerous because they contain harmful components." (Hall et al.	Since the statements within the comments are mainly based on CT results, please refer to answer n°1 to comment n°1. This is irrelevant, as the current Opinion is on the contribution of additives to the toxicity of cigarette smoke. Strictly speaking, the comment provided would only prove that additives are as toxic as tobacco. Otherwise, cigarettes with additives would be less harmful than cigarettes without additives. Please also refer to our general answer (n°1) on comparative testing. Whether or not most of the harm results from natural tobacco components is irrelevant here, as the current Opinion is on the contribution of additives to toxicity and addictiveness.

			2014) Moreover, based on epidemiological observations comparing so-called American Blend cigarette markets and Virginia cigarette markets, no differences in smoking-related diseases incidence has been established. In conclusion, no valid scientific basis justifies an additional battery of tests to compare toxic potentials of tobacco products with additives vis-à-vis absent of additives. p. 15, l.27 It is crucial that the concept of "addictiveness" is adequately defined and that "addictiveness" is objectively measureable before it may be considered as a basis for regulation. 6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion. A scientifically valid approach to evaluating the dependence potential of a given additive is not available up to now. p. 15, l.27 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed.	The term addictiveness has been further defined, although it was already specified in the previous Opinion (Tobacco I) and the definition included there was endorsed by the SC. Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
42.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.co	2.3.4 Information evaluation	Page 15, Lines 25-27: All methods that inform regulatory measures must be robust, reproducible, and repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence	Please note that the 2.3.4 Information evaluation refers to the methodology used by the SCHEER to draft the Opinion, not to the safety evaluation of the additives. The SCHEER has indeed asked to use, whenever possible, existing toxicological testing standards and assays recognised by bodies such as the OECD.

	m, United Kingdom		approach which includes reference to comparative toxicology.	Unfortunately for some end-points, methods alternative to animal testing are not yet available: in this respect the situation may be similar to the one experienced in the cosmetic area. The SCHEER agrees that validated methods should be the best choice; this is the reason why the SCHEER has pointed out the areas in which such validated tests are not available.
43.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.3.4 Information evaluation	We suggest deleting "attractive" (p.15, l. 27) and replace the sentence with "toxic and addictive effects, and characterizing flavours of tobacco additives" in line with Art. 6(2) TPD.	The suggestion has been accepted and the text has been changed accordingly.
44.	Vizée, Huub, delfortgroup, huub.vizee@delfortgroup.com, Austria	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	Step-wise approach: Opinion II states: • "the SCHEER concluded that a step-wise approach is the most pragmatic and efficient way to proceed in the assessment of the toxic, addictive and attractive effects of tobacco additives.". • "The order of the steps has been proposed in such a way to minimise testing" • "In order to limit the financial and administrative burden for industry and authorities" • "Whenever the evaluation of the additive in the unburnt form gives rise to any concern in relation to art 7 of the TPD (e.g. foreseeing the prohibition of additives having CMR properties) based on data collected in Step 1, the evaluation is stopped, meaning that the additive does not meet the requirement of the TPD. The same rule is applied to Step 2 for the pyrolysis products. In these cases, industry can proceed to step 4, reporting." Comment: Using the arguments to limit the financial and	The SCHEER disagrees with this interpretation: 'the argument to limit the financial and administrative burden for industry' is not

			administrative burden for industry and authorities to support the step-wise approach and minimise testing are false. Because of limited information retrieved by this approach the decision taken could be based on inconclusive evidence and should be avoided. It is not in the mandate of SCHEER to simplify the process of research, but to form an opinion based on sound scientific evidence, even when the financial and administrative burden for industry and authorities would be high.	cited to support the step-wise procedure but to encourage the formation of consortia. Whenever the data set of available data is inconclusive, the decision is not taken and further testing is required (Step 3). In case uncertainties cannot be reduced by comprehensive studies, risk reduction measures should immediately be applied in accordance with the precautionary principle and Article 7 of the TPD.
45.	Vizée, Huub, delfortgroup, huub.vizee@delfortgroup.com, Austria	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	Single individual additive Opinion II states: • "This procedure could be applied to single individual additives" Comment: The procedure should not be applied to single individual additives. 1. The mandate of SCHEER states: "The Committee is asked to consider in its assessment also the interaction with other ingredients contained in the products concerned and the emissions resulting from the combustion process involving the additive concerned as well as the intended use of the products." By concentrating on single individual additives, without looking at the interaction with other ingredients SCHEER is not fulfilling its mandate. 2. When step 2, pyrolysis, is carried out one should not concentrate on a single individual additive. Comparison studies should be carried out, whereby	The SCHEER disagrees with this interpretation: in this case single additive is opposed to groups of additives. Criteria for grouping were already included in the preliminary Opinion. Regarding the mixture toxicity, the issue is clearly described in the preliminary Opinion, addressing the comment. More specifically in mixture toxicity, the additive model [as opposed to synergistic and antagonistic ones] and a component approach, is proposed as the best pragmatic way to asses toxicity od mixtures, unless specific data are available indicating that a different model has to be used. In this specific case the effect of inhaling the additive itself, and its relevant pyrolysis products, is the contribution of the additive to the total toxicity of the tobacco smoke. Although there will potentially be synergistic or antagonistic effects of the additive and its pyrolysis products within the smoke matrix, as well as pyrosynthesis reactions, the net effect of all these contributions is too complex to study and assess with the currently available methodologies. Other than for additive effects, the current state of the art only allows assessing, very simple mixtures, not mixtures of thousands of components such as tobacco smoke. As a consequence, the SCHEER is aware that the possible interactions generated by reactions among ingredients can be underestimated, but proceeding pragmatically is the only way to go. Please see the previous answer, and regarding CT, please refer to answer n°1 to comment n°1.

			tobacco products with and without an additive should be examined and the results should be compared. It is clearly stated by the Commission that "an additive, essential for the manufacture of tobacco products, cannot be prohibited if it does not increase to a significant or measureable degree the addictiveness, toxicity or the CMR properties of the tobacco product." By neglecting comparative studies it is impossible to determine if an additive increases the addictiveness, toxicity or the CMR properties of the tobacco product to a significant or measureable degree and again SCHEER doesn't fulfil its mandate.	
46.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	The suggested evaluation of the pure pyrolysis product does not meet the requirements under Article 6 TPD2 that studies "take into account the intended use of the products concerned." Given that additives are intended to be used as part of cigarettes or RYO, they should be tested and pyrolised in a tobacco matrix. In 2.4.3.4, the Opinion states that "[t]here are hundreds of QSAR models, however the quality of reporting varies from model to model and predictivity must be assessed case by case". This undermines the stepwise model, as the only way to assess predictivity of each model is by progressing the subsequent steps in the process. Unless SCHEER is able to recommend a specific model, the reporting of which is of a sufficient and verified quality, the multiplicity of QSAR models negates the value of QSAR as a predictive tool in a stepwise process. SCHEER also alludes to the potential use of animal testing, despite the Union's objective to promote animal welfare (Article 13 TFEU) and to replace, reduce and refine animal testing (Directive 2010/63/EU). BAT does not endorse the use of	Regarding CT, please refer to answer n°1 to comment n°1. Furthermore, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Due to the different applicability domain typical for QSAR models, it is not possible to suggest a single fit for all models. Therefore the SCHEER reiterate that the most appropriate model should be evaluated on a case-by-case basis. The SCHEER is not endorsing performance of new animal studies in the Opinion. It is obvious that whenever data obtained on animal are already available they can be presented and are evaluated by the assessor by using a WoE approach. Only in very special cases could they be necessary: but the MS authority

			further animal testing, but considers that past studies may be used in order to apply "read-across" techniques for the identification of likely outcomes.	should be consulted before conducting them.
47.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	p.16, l. 2-4 SCHEER's coercive proposal to impose a burden of proof on manufacturers to prove that the "addictiveness" properties do not exist for any particular additive is inconsistent with the TPD2. Notably, article 6(2) and Article 7(9) simply require manufacturers to provide data on the properties of the relevant additives. Please retract the "burden of proof" constraint.	The wording 'burden of proof' has been replaced, although, please note that the regulatory requests for any other chemicals used for purposes other than tobacco additives is generally heavier and the 'burden of proof' that the chemical use is safe for the consumers is on Industry.
			p.16, l. 8 Again, it is noted that data provided by manufactures need to be evaluated for "attractive properties". Nonetheless "attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which member states may ban the use of additives. Please remove "attractiveness".	Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
			p.16, l. 22-23 SCHEER precisely concedes that direct information about the possible contribution of additives to "addictiveness" does not exist. The obscure notion recounting that "information can be derived from the mode of action of the additive" is thus hard to fathom. No scientific human study provides a definitive so-called mode of action of a single additive, via increased nicotine bioavailability or local anesthetic effects, with respect to smoking behavior or "addictiveness." Please amend: "it is possible" to "it may be possible."	This is why the SCHEER proposed a step-wise approach: Experimental testing of the dependence potential of tobacco additives is still limited due to the lack of validated administration models for the examined individual compound itself and in co-administration with other tobacco additives. In the proposed step-wise approach, the SCHEER discusses the possibilities to experimentally quantify the dependence potential of tobacco additives (often) co-administered with nicotine.
			p.17 Please note that pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis	The SCHEER reiterated its statement that pyrolysis is a useful technique for evaluating materials used at low levels, where it is unlikely that smoke chemistry assays could detect a change. To account for pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will

			models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement.	occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Indeed, pyrolysis is a semi-quantitative technique, but with the alternative use of smoke chemistry, subtle differences between the selected smoke components will not be noticeable. Given the complexity of cigarette smoke, it is difficult to identify individual materials that may result from the pyrolysis of ingredient mixtures unless radioactively labelled additives are used, but that method is sophisticated and expensive.
48.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. Pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. Page 16 Lines 13-25: To assess any potential for an additive to increase CMR properties of the product, the approach should be to undertake a study of the additive at levels used within the product (Art. 6.3), and identify whether any changes in the smoke profile are observed. If any changes are observed the effects on CMR properties should be compared in products with and without the additive. In addition, in Art. 6.3 it states that "studies shall also examine the interaction of the additive with other ingredients contained in the product concerned". Furthermore, the substantial amount of publicly available peer-	Regarding CT, please refer to answer n°1 to comment n°1. For this reason, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Again, please refer to answer n°1 to comment n°1.

			reviewed data (Baker, et al., (2004), Carmines et al., (2002), Gaworski et al., (1999), Gaworski et al., (1998). Gaworski et al., (2011), Renne et al., (2006)) has relevance for determining whether an additive increases the toxicity of the product. Additive specific testing should be focused on those iadditives for which there are no existing data at levels which are relevant to human exposure. In addition, a risk assessment of an additive added to a tobacco product, does not solely rely on data generated from smoke chemistry and biological testing of the additive in situ. Quantitative risk assessments are also carried on the single additive. Firstly, human exposure is calculated (using smoke transfer studies and upper bound consumption levels) and a risk assessment on the single additive is carried out based on that exposure. Using this approach together with smoke chemistry and associated biological data of the additive when combusted in a cigarette, gives a clear picture as to whether an additive will contribute to the toxicity of the product. It is unrealistic to consider all of the pyrolysis products of an individual additive, as the experimental pyrolysis process is not a realistic representation of the combustion process within a cigarette. Art 6.2(d) requires a comprehensive study of an additive to ascertain if it increases the CMR properties to a significant or measurable degree. This should be achieved through evaluation of smoke chemistry and subsequent biological effects. It is not valid to discount an additive based on individual assessment of decomposition products based on pyrolysis studies. Such studies have been repeatedly shown not to represent the fate of the additive within the product when combusted, and therefore is not representative under the conditions	This is the approach the SCHEER is proposing: Once the data are available on hazard identification and characterisation, the comparison with exposure would allow a risk assessment. The SCHEER reiterated its statement that pyrolysis is a useful technique for evaluating materials used at low levels, where it is unlikely that smoke chemistry assays could detect a change. To account for pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Indeed, pyrolysis is a semi-quantitative technique, but with the alternative use of smoke chemistry, subtle differences between the selected smoke components will not be noticeable. Given the complexity of cigarette smoke, it is difficult to identify individual materials that may result from the pyrolysis of ingredient mixtures unless radioactively labelled additives are used, but that method is sophisticated and expensive.

			required for the intended use (Art. 6.3). (Stotesbury et al., 1999; Purkis et al., 2011). The sole benefit of offline pyrolysis studies, is to estimate the potential of the additive to transfer intact, so that a risk assessment can also be performed on the exposure to the additive. Page 17, Lines 5 to 12: It should also be noted that there are six additives on the priority list that would not be able to be subjected to read across, as they are mixtures or natural additives (i.e. made up of multiple constituents).	The application of read across is a possibility to avoid testing, not an obligation. The SCHEER sees no inconsistency, considering that the step procedure is a general framework, and has to be adapted to the nature of the additive. In this line, it should be noted that whenever there is a good scientifically based and acceptable reason for a derogation to present data for a specific end-point, a justification can be provided (exactly as for any other regulatory requests). This is clarified in the revised version in the appropriate subchapter
49.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	We suggest deleting "Tobacco industry (…) and" (p. 16, l. 4- 6.) since this sentence does not reflect Art. 7 TPD but sets new rules not contained in the TPD (see our comments to section 2.1). Manufacturers and importers of cigarettes and roll-your-own tobacco containing an additive included in the priority list will be required to carry out comprehensive studies as per Art. 6 TPD and are not given "the burden of proof that an additive does not fall within the scope of the four categories mentioned in the terms of reference". Furthermore, we suggest replacing "toxic, addictive, and attractive" (p. 16, l. 8) with "toxic and addictive" since attractiveness is not a relevant criterion in Art. 6 and Art. 7 TPD. Since the DKFZ's proposal is not in line with Art. 6(2), (3) and 7(9) TPD (see in more detail our comment to the Abstract), it should not be taken as	Performing and submitting data necessary to evaluate the safety of the used additive is equivalent to have the burden of proof. The SCHEER disagrees that the sentence is not in line with TPD. The suggestion has been accepted and the text has been changed accordingly. The SCHEER step procedure took inspiration from the German Cancer Research Centre, but then it developed its own proposal. If the comment refers to CT, please see answer n°1 to comment

			a starting point. It follows that the paragraph "For the (…) 2010)." (p. 16, l. 13-25) should be deleted. While it is in line with Art. 7(6)(e) TPD to stop the evaluation in case data collected in step 1 shows that an additive has CMR properties in unburnt form (p. 16, l. 26-28), stopping the evaluation after step 2 in case any concerns arise (as suggested on p. 16, l. 29-30) would not allow to assess whether and in which quantities the additive increases the toxic or addictive effect, or the CMR properties of a tobacco products at the stage of consumption to a significant or measureable degree (Art. 7(9) TPD). Therefore, we suggest deleting "The same (…) reporting" (p. 16, l. 29-30). Instead of taking DKFZ's proposal as a starting point, we suggest a weight of evidence approach, i.e. not to stop evaluation after step 2 but always proceed to step 3 and to assess and weigh the results of all three steps. This weight of evidence evaluation or systematic review in risk assessment is promoted within different regulatory frameworks in the European Union, such as REACH - Regulation (EC) No. 1907/2006; Food and feed safety - European Food Safety Authority, 2010; Cosmetics - Regulation (EC) No. 1223/2009; Scientific Committee on Consumer Safety (2012). The weight of evidence approach is used to assess whole data sets by "summarizing, synthesizing and interpreting a body of evidence to draw conclusions e.g. regarding the relationship of a chemical exposure and adverse health effects" (Agerstrand et al., 2016). A "Memorandum on the use of scientific literature for human health risk assessment purposes – weighing of evidence and expression of uncertainty" adopted by SCENIHR (SCENIHR, 2012) provides	n°1. Please refer to our answer on CT, comment 1. The SCHEER already recommended evaluating all the available data based on a WoE approach. If the available data are robust enough to carry out an evaluation that could be taken as the basis for a decision (whatever it is), there is no need for further new testing. This was already reported in the preliminary Opinion (see page 19). There is no disagreement between the commenter, who may have misunderstood the Opinion, and the SCHEER. The issue has been further clarified in the revised version.

			guidelines on how to apply this weight of evidence approach "ensuring a high quality in all its risk assessments." We ask that these principles also be applied to the risk assessment of additives used in cigarettes and roll-your-own tobacco and that conclusions be drawn based on a body of evidence. We propose to change the whole section 3.4. to replace DKFZ's proposal with a weight of evidence approach and thereby align opinion 2 with the TPD, in particular Art. 6(2), (3) and Art. 7(9). The paragraph "In case of (…) tobacco industry." (p. 16, l. 33-36) is not necessary and should be deleted, since in this case the procedure should always go to the next step as already stated in lines 31-32, and the application of the precautionary principle has already been decided by the EU legislator when adopting the TPD.	The sentence on the application of the PP has been re-phrased (no mention to the PP is given) to avoid misinterpretations about risk management and inconsistencies with TPD.
50.	No agreement to disclose personal data	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	The proposal of performing pyrolysis tests with pure substances contradict to article 7(9) that "Member States shall, on the basis of scientific evidence, prohibit the placing on the market of tobacco products containing additives in quantities that increase the toxic or addictive effect, or the CMR properties of a tobacco product at the stage of consumption to a significant or measureable degree." It should be stressed that such a result can only be achieved by comparative studys and smoke analyses of tobacco products with and without additives. The pyrolysis experiments with pure substances might lead to completely different results as in combination with the tobacco matrix. Thus may lead to a ban of certain substances, which does not lead to a measurable and significant increase of products CMR potential. With exception of titanium dioxide 14 substances on the priority list are either natural mixtures or organic compounds.	Please refer to our answer on comment 1.

			It is inevitable that substances having CMR properties can be formed during the pyrolysis of these additives. According to the 2nd opinion of SCHEER the first step would lead to a ban of these additives without testing under real conditions. The results seems to be predetermined and without further investigations the priority list will become to a list of banned additives.	
51.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4 Step-wise approach	The main question of the SCHEER opinion is if a tobacco additive itself is able to produce toxic and / or CMR substances during pyrolysis. However, almost all organic substances produce toxic substances due to the process of pyrolysis. Because of widely known toxic properties of tobacco smoke the relevant issue for the assessment of a tobacco additive is that the usage of the additive does not increase the toxic properties of tobacco. The assessment of tobacco additives without the tobacco matrix and without quantitative considerations of the pyrolysis products is not the appropriate approach and would therefore terminate for all tested additives after step 2 (pyrolysis) of the recommended test strategy of this opinion. The recommended assessment strategy would not lead to an appropriate assessment of the additives.	The SCHEER agrees that tobacco smoke is toxic. Please refer to our answer on comment 1.
52.	Stoddart, Gilly, PETA International Science Consortium Ltd., GillyS@piscltd.org.uk, United Kingdom	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	In figure 1, under step 3 (testing), the second bullet point reads "in vitro / in vivo (including human)". This seems surprising, considering the Committee's preceding statements specifically not endorsing animal studies. In addition, line 8 contains the phrase "in order to limit the use of animal testing". These apparent discrepancies are eventually addressed in section 2.4.3.2, in which it is explained that in vivo tests may only be included in "exceptional cases". PISC urges the Committee to not endorse animal studies without exception. In	As noted by the commenter, the apparent discrepancies are eventually addressed in section 3.4.3.2, in which it is explained that in vivo tests may only be included in "exceptional cases". As requested it was indicated in the Figure legend, to address the concern by the commenter.

			this case, under step 3, the second bullet point would be changed to "in vitro / human" and the phrase in line 8 would be changed to "in order to limit testing". In the event the Committee allows the possibility of exceptions in section 2.4.3.2, it would be helpful to add a footnote to the figure legend explaining that in vivo tests may only be considered in exceptional cases. Likewise, the phrase in line 8 should be amended to read "in order to limit the use of animal testing to exceptional cases". Section 2.4.3.2 can also be cited.	The sentence in line 8 refers to REACH regulation, in which animal testing is not limited to exceptional cases, and therefore is not correct to change it.
53.	Marshall, Lindsay, Humane Society International, lmarshall@hsi.org, United Kingdom	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	We welcome this opinion as an opportunity to put a robust testing strategy in place that recognises relevant modern technologies, and that promotes in vitro and in silico testing. We see this as an opportunity to develop a regulatory framework that now includes a ban for in vivo testing of substances designed entirely for human pleasure. This strategy is timely and will be vitally important in the future assessment of electronic-cigarettes, given their rise in popularity. We note that Public Health England recently reported a recent all-time low in cigarette smoking in England, in part attributed to the increased use of electronic cigarettes. The opinion promotes a step-wise programme to provide exhaustive analysis of addictiveness and toxic potential additives for tobacco products. We would have no issues with the implementation of Step 1, since this phase aims to exploit the existing literature to identify data gaps on unburned additives. However, we are gratified to see the application of the emerging "Adverse Outcome Pathway" (AOP) methodology advocated, and we agree that the AOP approach represents the future of toxicology. We would like to see the relevant	Thank you for the positive comment.

			industries encouraged to generate AOP and to engage with the tools that the OECD makes available, including the AOP wiki and the AOP knowledge base for application in the near future and for the advancement of this field. As suggested in page 20, line 12, there are several AOP of relevance to additive testing that seem to permit analysis of groups of additives in terms of their molecular basis. The application of these approved AOP may allow further analysis of the likelihood of heritable DNA damage due to additive inclusion and removes any need for in vivo tests. We feel that, in the short term, it is more likely that literature studies will be used to identify previous studies/relevant data, but we would strongly advocate promotion of the use of existing AOP tools and industry-led development of novel and relevant AOP is a strategy to assess novel additives that replaces animal testing.	
54.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	The recommended assessment method is not suitable and the described stepwise approach not sufficient for the assessment of tobacco additives and would factually lead to the ban on all tested additives. The confusion as to the proper test under TPD2 to ban additives also appears to cross into the SCHEER's proposed methodology, with the SCHEER advocating pyrolysis testing of each priority list additive in isolation and explicitly warning against comparative studies. This guidance contradicts the relevant provisions of TPD2. As noted above, Article 6(2)(a) and (d) require the assessment of toxicity, addictiveness and CMR properties by reference to the relevant products and, on a similar basis, Article 7(9) only	The SCHEER ToR was to 'advise the Commission on the type and criteria for comprehensive studies that should be requested from manufacturers to assess the relevance of the individual additives'. Therefore the SCHEER based the Opinion on scientific ground; the SCHEER was not asked to evaluate the consequences due to the risk management measures taken afterwards. For CT, please refer to answer n°1 to comment n°1.

			bans additives that increase the toxicity, addictiveness or CMR effect of the product as a whole. Therefore, it is unclear how data that only relates to combustion of the additive in isolation would, of itself, further the purpose envisaged by TPD2. SCHEER appears to be limiting its recommendation to an assessment focused on the question of whether the tobacco additive in isolation - detached from tobacco – could form toxic substances or substances with CMR-properties during pyrolysis. In general, organic substances such as tobacco form toxic substances under pyrolysis. Because of the inherent and well-researched toxicity of tobacco smoke, the relevant issue for the assessment of a tobacco additive is that the usage of the additive under conditions of use should not increase the toxicity of tobacco smoke. The assessment of tobacco additives apart from the tobacco matrix and without quantitative considerations of the pyrolysis products is not an appropriate approach. The recommended test strategy - as presented in the current Preliminary Opinion - would terminate for all tested additives after step 2 (pyrolysis). The preliminary opinion of SCHEER therefore suggests that instead of an appropriate assessment including the product under conditions of use, an extensive ban of additives seems to be the objective of the recommendation. The aim of the assessment should be to ensure that "those additives do not result in a product with a characterising flavour and do not increase to a significant or measureable degree the addictiveness, toxicity or the CMR properties of the tobacco product".	The SCHEER agrees that tobacco smoke is toxic. Please refer to the answer to comment n°1. .

			The recommendation of the German standardization organization DIN, published in 2014, for a toxicity testing strategy of tobacco additives may be a valuable alternative. [Deutsches Institut für Normung DIN: DIN SPEC 10133: Toxicological assessment of additives for tobacco products – A guidance, 2004, Beuth Verlag.]	The document referred to is in essence a comparative testing approach. Please refer to our general answer on comparative testing.
55.	Bosse, Andrea, DVAI - German Association of the Flavour Industry, info@dvai-dvrh.eu, Germany	2.4 Step-wise approach to assess the toxic, addictive and attractive effects of tobacco additives	*Repetition of comment 51*	Please see the answer to Comment n°51.
56.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.1 Step 1: Evaluation of the additive in unburnt form	All the additives used in BAT products have undergone a formal risk assessment. This approach is aligned with best practice in many different areas, such as the World Health Organisation "Human Health Risk Assessment Toolkit" [48]. This starts with an evaluation of the ingredient involving a review of the available literature, which takes into account BAT's policy regarding the acceptability of additives, e.g. restricted use of CMRs (a position which predates TPD2). If no literature is available, in silico techniques, such as DEREK and Toxtree are used, and if appropriate "read across" of information from structurally similar compounds will be considered. If no toxicological issues or concerns are identified at this stage of the evaluation, further assessment is carried out.	The SCHEER welcomes the fact that TI already has a number of studies ready for submission, and has already performed a formal risk assessment. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, also in view of the SCHEER indication about CT. This situation seems to facilitate the work by TI in complying with the requests.
57.	Simms, Liam,	2.4.1 Step	Page 18, Lines 16 to 25:	Step 1 is related to the unburnt form, therefore the comment is

	Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	1: Evaluation of the additive in unburnt form	In the case of complex mixtures such as naturals, transfer of components is difficult to measure and accordingly, this is why a complete review of the impact on the smoke chemistry and the biological impact of these additives is most relevant to the risk assessment. This approach is in line with Art. 6.3 of the Directive, which states "…studies shall take into account the intended use of the products….". Page 18, Lines 37-38: SCHEER states that "…menthol, which is functionally closely related to e.g. menthol derivatives, wintergreen and spearmint". It should be noted that both wintergreen and spearmint oils contain minimal amounts of menthol and related compounds. Methyl salicylate and Carvone are the most abundant compounds, respectively, in these flavours. Both methyl salicylate and Carvone have different flavours and physicochemical properties to menthol. We therefore recommend that SCHEER reviews its source materials and is cautious in its interpretation of chemical read across. We agree with SCHEER's recommendation on the use of read across approach, for situations where data gaps exist. For chemical read-across, it should be noted that EFSA (2014) states that as it is a "..non-formalised approach, it requires considerable expert knowledge and judgment". We recommend that this statement is taken into consideration.	not appropriate. The suggestion has been accepted and the example has been deleted. Thank you for the positive comment. However, consideration about the expertise of the assessor is valid for any regulatory area and does not depend on the SCHEER to judge it.
58.	May, Anne, Philip Morris International Management SA, anne.may@p	2.4.1 Step 1: Evaluation of the additive in unburnt form	We suggest deleting "(and other possible factors contributing to attractiveness)" (p. 18, l. 33) since attractiveness is not a relevant criterion under Art. 6 and 7 TPD.	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

	mi.com, Other			
59.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.1.1 Collection of literature data	BAT already conducts comprehensive searches of all available toxicological information, and excluding the use of formally classified genotoxicants, non-threshold carcinogens, mutagens, reproductive and developmental toxicants as additives, BAT toxicologists select the most relevant studies for evaluation for the intended route of exposure. To do this, the quality of all pertinent studies identified is evaluated, using an assessment of its relevance and reliability as well as the adequacy of the information for hazard/risk assessment purposes, following the principles described by Klimisch et al. (1997) [9]. We refer to our comments to Section 2 concerning SCHEER's reference to the alleged attractiveness of additives.	The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance (also based on the Klimish score, as already indicated in the preliminary Opinion) in view of the SCHEER indication about CT. This situation seems to facilitate the work by TI in complying with the requests. Please see the answer provided there.
60.	Simms, Liam, Imperial Tobacco Limited, liam.simms@ uk.imptob.co m, United Kingdom	2.4.1.1 Collection of literature data	Page 20, Lines 5-9: We agree with SCHEER's recommendation on the use of read across (where appropriate to the additive under consideration) and a weight of evidence approach, for situations where data gaps exist. For chemical read-across, it should be noted that EFSA (2014) states that as it is a "..non-formalised approach, it requires considerable expert knowledge and judgment". We recommend that this statement is taken into consideration. Additionally, the OECD (2010) states that the person providing the "…scientific judgment must have expertise concerning the relevant endpoint(s) and study methods". We are in agreement with this guidance. It should also be noted that there are six additives	Thank you for the positive comment. However, consideration about the expertise of the assessor is valid for any regulatory area and does not depend on the SCHEER to judge it. The application of read across is a possibility for avoiding testing,

			on the priority list that would not be able to be subjected to read across, as they are mixtures or natural additives (made up of multiple constituents). Page 20, Line 8: There appears to be an error in this section as SCHEER draws reference to "section 3.4.1.1", a section missing from Preliminary Opinion 2. Page 20, Lines 11-13: We are closely monitoring developments in the field of Adverse Outcome Pathways (AOPs). We recommend that only AOPs that have been reviewed, validated and endorsed by the OECD are used.	not an obligation. The SCHEER sees no inconsistency, considering that the step procedure is a general framework and has to be adapted to the nature of the additive. Thank you for highlighting the typo, it has been corrected. No disagreement with the SCHEER Opinion. See page 20.
61.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.1.1 Collection of literature data	Since attractiveness is not a relevant criterion under Art. 6 and 7 TPD, we suggest to - replace "their attractiveness and addictiveness" (p. 18, l. 42-43) with "addictiveness and whether, and at what level, additives result in a characterizing flavor other than tobacco"; - delete "and attractiveness" (p. 20, l. 10); and - delete "Accordingly, the same apply to attractiveness investigation (for details see paragraph 3.4.3.6)" (p. 20, l. 24-25). As duly noted by SCHEER, Adverse Outcome Pathway (AOP) is an emerging approach (p. 20, l. 11). However, up to now, AOPs are not used outside of toxicology. The main reason for this may be that in toxicology various in vitro assays for different toxicological endpoints are developed, historical data are available in data base, and in silico models like quantitative structure–activity	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". The wording has been revised. See above.

			relationship (QSAR) are implemented. The same amount of knowledge is not available for addictive substances. Some in vitro assays to measure the addictive potential are implemented for initial screening and further investigation of neat compounds during the drug development process. However, the process of cigarette smoke addiction with its multiple, and varying factors is not fully understood and in vitro methods how to measure the addictive potential of tobacco additives are not available. For this reason we believe that AOP is currently not suited for determining addictiveness and we propose deleting "AOP methodology may be useful (…) Toxicogenomics." (p. 20, l. 21-32). However, we encourage SCHEER to trigger the development of relevant research, in line with the Committee's expressed interest at p. 69, l. 25-26 ("It is advised that independent bodies or organisations begin conducting relevant research"). We would welcome any opportunity to contribute to this research and method development. In the meantime, we will carry out and report on studies using the best currently available methods. We suggest adding "(cigarette/roll-your-own)" after "products concerned" (p. 20, l. 40) the same way it is included in l. 45 to clarify that "products concerned" under a) means the same as "products concerned" under d).	The wording has been revised. Reporting on research need was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted. A paragraph has been added at the end of Chapter 4. This was further specified whenever considered relevant in the final Opinion.
62.	Marshall, Lindsay, Humane Society International, lmarshall@hsi	2.4.1.1 Collection of literature data	As described in the Opinion, the application of Organisation for Economic Co-operation and Development (OECD) guidance to group chemicals and subsequent use of AOP should be sufficient to address this issue. As referenced in the Opinion (Kienhuis et al., 2016), in vitro methods combining	Thank you for the positive comment.

	.org, United Kingdom		cytotoxicity, toxicogenomics and microarray data have been used with some success for developing a risk assessment strategy for tobacco products and this regime could be applied to novel additives.	
63.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.4.1.2 Evaluation	p. 20, l. 21-22 The SCHEER refers to an AOP in the context of a regulatory framework suggesting that an "AOP methodology may be useful in elucidation of molecular basis for addictiveness of tobacco products." Please add that the AOP framework has never been designed to collect data on "addictiveness" or "attractiveness". Please mention that Villeneuve & Garcia-Reyer, who addressed AOP in the context of "Predictive Ecotoxicology" underscored that "A fully developed AOP is synonymous with a mechanism of action—a complete and detailed understanding of each and every step in the sequence of events leading to a toxic outcome." Please mention that the authors refer to several limitations: e.g., "Adverse outcome pathways, and the toxicity pathways they encompass, are based on the assumption that an environmental or chemical disturbance is severe enough to overwhelm an organism's adaptive mechanisms and drive the response trajectory to adversity. Please mention that AOPs are informative for hazard assessment but more limited in their application to risk assessment. An AOP does not account for contributions of chemical dose or concentration, timing and duration of exposure, biotransformation, or an organism's adaptive capacity." Please add that Ankely et al., cited by SCHEER, comment that: "In and of themselves, AOPs cannot take into consideration all of the potential biological interactions that may determine whether an initiating event will drive the system, uninterrupted, to the adverse outcome." Taken together, the use of AOP in the context of a	The suggestion has been accepted and the text has been changed accordingly. It is not the focus of the Opinion to describe in details pros and cons of the AOP approach.

			regulatory framework, i.e., in the context of "addictiveness" and "attractiveness" is poorly founded and immature. Moreover, SCHEER refers for details to paragraph 3.4.3.5. We could not locate this paragraph in the whole document. p.20, l. 39-41 Please delete "contributing to the toxicity or addictiveness of the products concerned…" This is not a requirement of the TPD2 article 7, as stated incorrectly by SCHEER. p.20, l.24-25 With respect to 'attractiveness' investigation, SCHEER refers for details to paragraph 3.4.3.6. We could not locate this paragraph in the whole document. Nonetheless attractiveness is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which member states may restrict the use of additives. Please remove this sentence related to "attractiveness". p.20, l.44 Please delete 'Leading to the formation of substances that have CMR properties' as the guidance provided by SCHEER goes beyond requirements as defined in of the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation. Moreover, many additives are organic, and as such,	The typo has been corrected. The wording has been changed. The typo has been corrected. Attractiveness has been replaced with the appropriate terms. Please refer to Article 7 of Directive 2014/40/EU, which foresees in particular **the prohibition of the following**: 1) tobacco products with a characterising flavour (Art 7(1)) 2) tobacco products containing the following additives2 (Art 7(6)): a) vitamins or other additives that create the impression that a tobacco product has a health benefit or presents reduced health risks; b) caffeine or taurine or other additives and stimulant compounds that are associated with energy and vitality; c) additives with colouring properties for emissions; d) for tobacco products for smoking, additives that facilitate inhalation or nicotine uptake; and **e) additives that have CMR3 properties in unburnt form.** On this basis, the SCHEER only concludes based on the TPD. Whenever, necessary, this has been clarified re-wording the sentences.

			it is reasonable to expect the formation of toxicologically relevant pyrolysis products. Under such circumstances it would be illogical to expect a completely inert material. Please refer to Dempsey et al., 2011, DIN, 2014	
64.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.1.2 Evaluation	Page 20, Lines 34-36: Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. If in silico data or read-across data produces an in silico alert for CMR, a weight of evidence approach should be used comparing in vitro and currently available animal testing data to determine whether an additive has CMR properties or not. An in silico alert for CMR alone would not be sufficient to determine a CMR, due to the relative high false-positive predictions of in silico techniques (Serafimova et al., 2010).	Please see answer n°1 to comment n°1 concerning CT There is no disagreement between the commenter and the SCHEER, who suggested a WoE approach for the evaluation of data coming from Step 1 and 2 first and if not robust enough, combined with results coming from Step 3.
65.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.1.2 Evaluation	We suggest the sentence on p.21, l.2-4 "In case" is deleted as the precautionary principle application is not in line with the TPD and as testing should always proceed to Step 3.	The sentence on the application of the PP has been re-phrased (not mentioning the PP) to avoid misinterpretations about risk management and inconsistencies with TPD.
66.	Thielen, Anja, Deutscher Zigarettenver	2.4.1.2 Evaluation	*Repetition of comment 11*	Please see the answer to Comment 11.

	band, a.thielen@zigarettenverband.de, Germany			
67.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.1.2 Evaluation	*Repetition of comment 11*	Please see the answer to Comment 11.
68.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United Kingdom	2.4.2 Step 2: Evaluation of the pyrolysis products	The Opinion calls for "realistic" experimental conditions for the pyrolysis studies (p.21:10). Pyrolysis of the pure additive is not realistic, and in accordance with concern shown for pyrosynthesis products, different smoke components are more likely to be formed in a tobacco matrix than by the pure additive. Pyrolysis of the pure additive is also inconsistent with the requirement in TPD2, Article 6 para. 3 that the studies shall take into account the intended use of the products concerned and examine in particular the emissions resulting from the combustion process involving the additive concerned. We refer to our comments to Section 2 concerning SCHEER's reference to the alleged attractiveness of additives.	Please see the answer on comparative testing (n°1). Furthermore, regarding pyrosyntheis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".
69.	Martinez, Javier, JT International	2.4.2 Step 2: Evaluation of the	SCHEER suggests pyrolysis testing of each priority list additive in isolation, and advises against comparative studies of the final tobacco product	The SCHEER reiterated its statement that pyrolysis is a useful technique for evaluating materials used at low levels, where it is unlikely that smoke chemistry assays could detect a change. To

	SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	pyrolysis products	comprising the relevant additive. SCHEER concludes that if pyrolysis of a single additive generates compounds with CMR properties, this additive will not meet the TPD2 requirements and will be banned. Studies on tobacco additives demonstrate that the utility of pyrolysis model systems lies mainly in distinguishing between those compounds that transfer intact into the mainstream smoke of cigarettes from those that might be liable to degrade. Pyrolysis does not provide a robust prediction of the compounds that might be formed from additives during cigarette smoking. Although pyrolysis degradation products may give some qualitative indication of the products that may be formed during cigarette combustion, pyrolysis should not be used for a quantitative measurement, but rather to provide a gross overestimate of degradation products (Baker & Bishop 2005) that might appear in cigarette smoke. Therefore it does not provide data that can be directly correlated with cigarette smoke. The guidance of SCHEER is at odds with the wording of the TPD2. Article 6(2) (d) indicate that the manufacturer should examine, by means of its comprehensive studies, whether a relevant additive "…has the effect of increasing the CMR properties in any of the products concerned to a significant or measurable degree". The approach taken in the opinion is also inconsistent with Article 7(9), which prohibits "the placing on the market of tobacco products containing additives in quantities that increase the toxic or addictive effect, or the CMR properties of a tobacco product at the stage of consumption to a significant or measureable degree." This suggests that the ultimate purpose of the testing data provided pursuant to Article 6(2) (d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, "addictiveness" or	account for pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products").

			CMR properties upon consumption of the final tobacco product (as opposed to the mere presence of those properties upon combustion of that additive in isolation). Therefore, it is unclear how data that only relates to combustion of the additive in isolation would, of itself, further the purpose envisaged by the TPD2. JTI believes that a pragmatic and comprehensive evidence-based approach is needed in order to assess tobacco additives. However, the proposals brought forward by SCHEER is likely to ban all prioritized additives in Step 2. SCHEER suggests that an additive should be banned, if the pyrolysate of the pure additive contains any substances with CMR properties (the suggested threshold appears to be the limit of detection). 14 out of the 15 prioritized additives are organic substances or mixtures which, during pyrolysis, inevitably will form some amount of constituents with CMR properties. This makes it unlikely that any of the priority additives will pass the criteria defined by SCHEER. JTI believes that pyrolysis studies should be considered as one source of information - with limitations - in a wider assessment model, which should include comparative tests where prototype products with and without specific additives are analyzed for significant differences in smoke composition or for toxic effects in accordance with Article 7(9) of the TPD2, to reflect the final tobacco product as a whole during combustion under conditions of use. JTI has submitted on a regular basis pyrolysis data and, comparative test results for tobacco additives to EU Member States in accordance with the TPD1.	
70.	Simms, Liam, Imperial Tobacco Limited,	2.4.2 Step 2: Evaluation of the pyrolysis	Page 21, Lines 6-17: Pyrolysis is a technique that has been applied by many of the major tobacco companies to characterize neat additives. The main benefit of	The SCHEER reiterated its statement that pyrolysis is a useful technique for evaluating materials used at low levels, where it is unlikely that smoke chemistry assays could detect a change. To account for pyrosynthesis, the SCHEER proposed in the Opinion

	liam.simms@uk.imptob.com, United Kingdom	products	using pyrolysis data is to identify whether an additive will transfer intact or undergo significant degradation in a burning cigarette (Purkis et al., 2011). Where degradation is indicated, pyrolysis has sometimes been used to investigate possible break down compounds which may occur during smoking of a cigarette. Many of the degradation compounds detected in pyrolysis experiments may not be formed during combustion in tobacco due to competing reactions between the combustion products of the tobacco and the additives (Hahn et al., 2010; Roemer et al., 2010; Intorp et al., 2010; Purkis et al., 2011).The evidence shows that there is no correlation between the results of pyrolysis experiments and the smoke chemistry, therefore Pyrolysis is inadequate to assess how an additive behaves in a burning cigarette (Hahn et al., 2010; Purkis et al., 2011). Numerous publications have also highlighted the lack of impact that additives added to tobacco have on the chemical composition and the toxicity of smoke (Gaworski et al. 1998; Roemer et al.2002 ; Baker et al.,2004 etc). A notable example is glycerol, investigated by Roemer et al (2010). Even when glycerol was added to cigarettes at significant quantities (0, 1.5, 3.3, 5.5% by weight), none of the compounds predicted by pyrolysis, such as acrolein, could be detected at higher levels in the smoke under ISO conditions. To assess how tobacco additives influence the quantitative levels of toxic substances in whole smoke, the pyrolysis of additives is not suitable as	(paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). Indeed, pyrolysis is a semi-quantitative technique, but with the alternative use of smoke chemistry, subtle differences between the selected smoke components will not be noticeable. Given the complexity of cigarette smoke, it is difficult to identify individual materials that may result from the pyrolysis of ingredient mixtures unless radioactively labelled additives are used, but that method is sophisticated and expensive.

			an assessment criterion (Hahn et al., 2010).	
71.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.2 Step 2: Evaluation of the pyrolysis products	We suggest deleting ", attractiveness" (p. 21, l. 11) since attractiveness is not a relevant criterion under Art. 6 and 7 TPD. Furthermore, we suggest adding "The data will be used as one of the elements considered in the weight of evidence approach" after "in the unburnt form" (p. 21, l. 13) as further explained in our comment to section 2.4.	The suggestion has been accepted and the text has been modified accordingly.
72.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United Kingdom	2.4.2.2 Pyrolysis studies (if needed)	Whilst the Opinion accepts that "analysis of selected smoke components is described for many different additives" {p.21:22-24}, it fails to reference Baker et al.(2005) [5] paper, which provides data for Carob bean, cocoa, fenugreek, fig extract, guar gum and liquorice, all of which are included on the Priority List. The Opinion takes the studies it refers to out of context, casting doubt on Baker's experiments as the heating rate "seems rather slow" { 22:25}. This limitation reflects the maximum heating rate that was technically achievable at the time of the experiment and remains for commercially available pyrolysis instruments. The approach reported by Baker et al [4] was to mimic the temperature, oxygen concentration and flow/heating rates as closely as possible to those of a burning cigarette both in the smouldering and combustion phases. Pyrolysis was carried out by ramping from 300°C to 900°C, temperatures which were reported by Baker in his paper, "A review of pyrolysis studies to unravel reaction steps in burning tobacco" [61], to be representative of the temperatures experienced in the burning zone of a cigarette and to allow other distillation and condensation processes to occur. In	The SCHEER reiterate its statement that pyrolysis is a useful technique for evaluating materials used at low levels, where it is unlikely that smoke chemistry assays could detect a change. To account for pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). Indeed, pyrolysis is a semi-quantitative technique, but with the alternative use of smoke chemistry, subtle differences between the selected smoke components will not be noticeable. Given the complexity of cigarette smoke, it is difficult to identify individual materials that may result from the pyrolysis of ingredient mixtures unless radioactively labelled additives are used, but that method is sophisticated and expensive.

			the same paper evidence was presented that isothermal pyrolysis experiments overestimated the thermal degradation of some components and that temperature ramped pyrolysis therefore simulated most closely the variety of mechanisms occurring during combustion within a cigarette. Therefore, isothermal pyrolysis is unnecessary, because it does not reproduce the processes occurring in the burning cigarette, and so is at odds with producing data which is "relevant for tobacco smoking", a factor which is repeatedly stated as being the most important. The use of other thermal gradients to investigate the pyrolysis of tobacco (e.g. 5°C/min and 20°C/min) has been reported [62]. SCHEER suggests that "each additive is to be studied under different reaction regimes (inert and 2-14% oxygen)" {p.22:38-39}. However, smoking and combustion of tobacco always occurs in the presence of oxygen and hence the purpose of repeating the experiments in an inert atmosphere is unclear. Furthermore, pyrolysis of the pure additives would fail to account for products of pyrosythesis reactions, to which SCHEER seems to attribute great significance. SCHEER's focus on determining "whether the additive is a precursor or a catalyst for the formation of a certain smoke component" {p21:30-31}, rather than studying a realistic sample of the smoke inhaled by a tobacco user is also questionable. There is also evidence to suggest that pyrolysis of the pure additive would not provide a robust prediction of the compounds that are formed from ingredients during cigarette smoking, and so would fail to take into account the intended use of the additive, as required by Article 6 TPD2 [17].	This is well explained in Paschke et al 2016: Even at the maximum temperature of up to 900–1000 °C, only a portion of the respective additives may be affected, although an inert and/or oxidative partial thermal disintegration is already initiated at temperatures far below this. See above.

			Pyrolysis-gas chromatography is a qualitative technique and is unsuitable for the quantification of substances. To quantify accurately the amount of a substance observed during pyrolysis it is necessary to introduce calibration standards into the gas chromatograph. This is technically impracticable because pyrolysis GC/MS systems are not designed to de-couple, and moreover, calibration standards would be required for all possible pyrolysis products, which makes such analysis utterly impracticable – particularly when the time frame for reporting such results is limited. The commercial availability of authentic pure standards of pyrolysate products for use as analytical standards is also very limited, and there is no advice in the document on how to assess components for which no authentic standard is available.	See above.
73.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.4.2.2 Pyrolysis studies (if needed)	p. 21, l. 34-35. The limitations of the pyrolysis model, i.e., resulting in an over prediction of what occurs in the burning cigarette, should also be highlighted in this section. Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different results, quantitation at this stage might be a misleading approach as it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement. Moreover, SCHEER's proposed methodology conflicts with its own assertion that: "… the [proposed] pyrolysis conditions only approximate the burning	See our answer(s) to the previous comment.

			cigarette…and make no allowance for the presence of other tobacco and/or smoke components that may interact with the additives. Pyrosynthesis processes related to the tobacco matrix will not occur when the additive is pyrolysed as a single component outside of the tobacco matrix." Please refer to the recent study authored by Dr. Meike Paschke et al. (2016), affiliated to the German Federal Institute for Risk Assessment. While, in principle, pyrolysis processes are difficult to define, the authors performed an on-line pyrolysis technique coupled to gas chromatography-mass spectrometry to identify the pattern of chemical species formed upon thermal decomposition of 19 different tobacco additives like raw cane sugar, licorice or cocoa. The formation of 20 PAHs was monitored for cocoa. Notably, the authors embraced here the comparative testing strategy, as the results obtained were compared to additive-free tobacco, and mixtures of additive-free tobacco with cocoa, all of which were pyrolyzed at the same conditions. The results indicate that the adding of cocoa to tobacco had no influence on the relative amounts of the PAHs formed. The authors caution, however, that "this method is not suitable to analyze emissions in relation to individual puffs or standardized smoking conditions." Notably, the authors comment that "Besides additional toxic emissions, pyrolysis of additives or ingredients should not increase the overall toxicant levels in emissions, since this potentially leads to increased toxicity according to the provisions of article 7."	The SCHEER is aware of this study and it indeed exactly demonstrates our point that comparative testing design will not pick up subtle differences, even when adding large amounts of additives.
74.	Simms, Liam, Imperial Tobacco Limited,	2.4.2.2 Pyrolysis studies (if	Page 22, Lines 42-44: Pyrolysis cannot be used as a quantitative measurement method. Instead it may provide a	Please see the answer to comment 72.

	liam.simms@uk.imptob.com, United Kingdom	needed)	crude indication of the types of degradation products that might occur when an additive heated, which can be used as a pointer for further investigation. It does not, however, provide data that can be directly correlated with cigarette smoke (Purkis et al 2011). Some industry data also includes mass balance studies – i.e. the inclusion of additives often incorporating labelled compounds to find out how much transfers to mainstream or sidestream smoke versus the residual quantity in the ash or that retained by the filter. In these studies there was often a large proportion of the additives that could not be accounted for (i.e. they were not detected in the side stream smoke, ash, cigarette butt. They did not increase or lead to higher levels of so called "Hoffman analytes" (smoke constituents). In radiolabelled studies the majority of breakdown products from semi volatile and non-volatile additives were not products of incomplete combustion, but products of full combustion, particularly CO and CO2 (Purkis et al., 2011). This goes to explain why such additives were not significantly adding to the Hoffmann analytes, rather they were undergoing full combustion in a cigarette, and these conditions are not replicated in pyrolysis studies (Roemer et al. 2010; Purkis et al., 2011). Crucial to the assessment of a tobacco additive is the evaluation of tobacco smoke from cigarettes, both with and without the additive included. The key determinants are both the relative increase of any chemicals of concern (e.g. Hoffman analytes) in the smoke chemistry and assessment of exposure in a biologically relevant system (Page 23 lines 13 and 14)(Hahn et al., 2010). Over 90% of the weight of	

			a cigarette is made up of tobacco, and studies show tobacco additives do not generally influence the composition or the overall CMR properties of tobacco smoke when tested by a relevant biological system.	
75.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.2.2 Pyrolysis studies (if needed)	In this section, pyrolysis testing is partly confused with smoke chemistry studies. The methodology described on p. 21, l. 18-31 is not a pyrolysis study but a smoke chemistry study. Furthermore, opinion 2 refers to a number of lists of harmful and potentially harmful smoke constituents and recommends these to be identified with pyrolysis studies (p. 22, l. 45 – p. 23, l. 14). However, most of these constituents cannot be identified with pyrolysis studies but with smoke chemistry studies. For this reason and to avoid confusion we recommend to either move the parts dealing with smoke chemistry studies (cited above) in a separate section as part of Step 3 or delete them. On p. 22, l. 36-44 SCHEER recommends a broad range of experimental conditions. However, the recommendation is too broad and not specific enough that it could be applied by the industry. We kindly ask SCHEER to provide a more specific description of the pyrolysis method the industry should apply (please specify instrument parameters, heating rate, pyrolysis temperature, mass range (m/z), oxygen content, GC column). We would recommend to use Baker 2004, the use of which is well and widely documented. In a publication currently in press, the German Federal Institute for Risk Assessment (BfR) (Paschke, 2016) assesses "methods to record and monitor patterns of pyrolysis products of all	The comment has been accepted and the first sentence was modified by replacing the word pyrolysis studies by smoke chemistry. From the ToR: *The Committee is asked to advise the Commission on the type and criteria for comprehensive studies that should be requested from manufacturers to assess the relevance of the individual additives,….* The SCHEER was not therefore asked to provide detailed protocols. Considering the nature of the products, some tests can be relevant and others not. As for any other regulatory area, it is possible that whenever there is a good scientifically based and acceptable reason for a derogation to present data for a specific end-point a justification can be provided (exactly as for any other regulatory requests). This is clarified in the revised version in the appropriate subchapter (page 24). The SCHEER is aware of this study and it indeed exactly demonstrates our point that comparative testing design will not pick up subtle differences, even when adding large amounts of additives, such as the cocoa used in this study.

			relevant additives in use" to comply with Art. 5 TPD reporting requirements. The BfR suggests that on-line oxidative and inert pyrolysis could also be an appropriate tool for the detection and qualitative assessment of degradation products of tobacco additives under smoking conditions. Furthermore, the BfR recognizes that pyrolysis can only be a "first step" in the assessment (p. 2) and that: "[t]o further assess the toxic or addictive potential of the examined additives quantitative studies would be necessary though" (p. 11). Similarly, we recommend to include in step 3 smoke chemistry and in vitro tests (see DIN and Health Canada discussed in 2.4.3.4).	
76.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.2.2 Pyrolysis studies (if needed)	The assessment of tobacco additives shall be done based on the tobacco matrix; pyrolysis studies are only one element of the testing a tobacco additive. In chapter 2.4.2.2, SCHEER discusses the complexity of the combustion process and notes that pyrolysis cannot reflect the behavior of an additive in the burning cigarette. As an additional point there are no generally accepted standardized methods available for pyrolysis and SCHEER concludes that there are no technical parameters for pyrolysis which reflects the situation in a burning cigarette. Nonetheless, SCHEER rely upon pyrolysis as a sole tool for assessing the burnt additive and rejects the tobacco matrix for additive testing. Pyrolysis is useful as a first screening of potential pyrolysis products and therefore it may be reasonable to conduct or refer to pyrolysis data for the assessment of tobacco additives. However, pyrolysis alone is not sufficient for the assessment of tobacco additives that are burnt during consumption like in a burning cigarette. The nature	Please see the answer to comment 72.

			and quantity of the pyrolysis products greatly depend on the conditions of the parameters of the pyrolysis. Therefore, it is essential to validate pyrolysis data by evaluation whether these pyrolysis products are actually found in the smoke when the additive is present in the tobacco product.	
77.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.2.2 Pyrolysis studies (if needed)	The assessment of tobacco additives should include the tobacco matrix; pyrolysis of the additives alone could only be used as screening parameters of the assessment. The nature and the quantity of the pyrolysis products depend on the conditions of the pyrolysis especially the interactions with the tobacco matrix. Therefore the effect of additives in a burning cigarette can only be tested by the chemical analysis of tobacco smoke and the comparison between a cigarette without and a cigarette with the tested additive. Tobacco smoke is a well-researched mixture of substances for which established and standardized methods [1] are available and should be included as a test agent. [1] ISO 3308, Routine analytical cigarette-smoking machine — Definitions and standard conditions. Borgerding, M. F., Bodnar, J. A., and Wingate, D. E. The 1999 Massachusetts Benchmark Study — Final Report; presented to the Massachusetts Department of Public Health. 24-7-2000. Available at: http://legacy.library.ucsf.edu/tid/yek21c00	Please see previous answer to the same topic (e.g. n°72).
78.	Bosse, Andrea, DVAI - German Association of the Flavour Industry, info@dvai-dvrh.eu,	2.4.2.2 Pyrolysis studies (if needed)	*Repetition of comment Nr 77*	Please see the answer to comment n°77.

	Germany			
79.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.2.3 Evaluation	SCHEER states "if it is demonstrated that compounds proven to have CMR properties are generated from pyrolysis of an additive, this additive will not meet the TPD requirement." There seems to be no such requirement in the TPD2. If SCHEER is referring to Article 7 with this statement, it acts beyond its Terms of Reference. The toxicity of any substance must be related to quantified exposure and is not absolute [sola dosis facit venenum]. A true measure of exposure is only realistically achievable through the use of comparative studies which will replicate real life levels of additives and actual transfer rates into smoke. [63] SCHEER refers to the precautionary principle. There is simply no scope for applying the precautionary principle in the context of Article 6, which is concerned with the scientific exercise of carrying out comprehensive studies in relation to a number of additives contained in a priority list, so as to comply with the enhanced reporting obligations on these additives. Article 6 TPD2 is not concerned with any bans or limitations on these additives, which is the purview of Article 7 of TPD2 and fall outside SCHEER's Tterms of Rreference.	The comment has been accepted and the text has been modified accordingly. For CT, please refer to answer n°1 to comment n°1. The sentence on the application of the PP has been re-phrased (not mentioning PP) to avoid misinterpretations about risk management and inconsistencies with TPD.
80.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva,	2.4.2.3 Evaluation	p.23, l.23-25 Please delete: "For instance, if it is demonstrated that compounds proven to have CMR properties are generated from pyrolysis of an additive, this additive will not meet the TPD requirement." The guidance provided by SCHEER goes beyond requirements as defined in of TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include	The comment has been accepted and the text has been modified.

	Switzerland, Javier.Martinez@jti.com, Other		reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation.	
81.	Henkler, Frank, German Federal Institute for Risk Assessement (BfR), frank.henkler@bfr.bund.de, Germany	2.4.2.3 Evaluation	The BfR does strongly agree with SCHEER that animal studies aimed to evaluate the safety on tobacco additives are ethically questionable. In fact, such studies are pro-hibited by the German Animal Welfare Act, but not by the European Tobacco Product Directive 2014/40/EU. This is a marked difference to the regulation of cosmetic prod-ucts. Although European regulators should not request in vivo data from manufactures or importers, it should still be possible for competent authorities to consider available animal data in assessments of both tobacco additives and products. This should be clarified in section 2.4.3.2 on page 25. Further, human studies should also be acceptable to address other aspects of attractiveness, besides flavor assessments.	Thank you for the positive comment. This is addressed in the revised text of the final Opinion.
82.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.2.3 Evaluation	Page 23, Lines 20-28: Pyrolysis cannot be used as a quantitative measurement method. Instead it may provide a crude indication of the types of degradation products that might occur when an additive heated, which can be used as a pointer for further investigation. It does not, however, provide data that can be directly correlated with cigarette smoke	Please see the answer to comment 72.

			(Purkis et al 2011). Where degradation is indicated in transfer studies, pyrolysis has sometimes been used to investigate possible break down compounds which may occur during smoking of a cigarette. Many of the degradation compounds detected in pyrolysis experiments may not be formed during combustion in tobacco due to competing reactions between the combustion products of the tobacco and the additives (Hahn et al., 2010; Roemer et al., 2010; Intorp et al., 2010; Purkis et al., 2011).The evidence shows that there is no correlation between the results of pyrolysis experiments and the smoke chemistry, therefore Pyrolysis is inadequate to assess how an additive behaves in a burning cigarette (Hahn et al., 2010; Purkis et al., 2011). Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. SCHEER's recommendation for manufacturers/importers to use the precautionary principle goes beyond the remit of Art. 6 of the Directive. It should be deleted as it is a preventative decision-taking approach to risk management. Due to the known health risks of smoking, we do not claim that tobacco products are "safe", neither do we make claims that any Tobacco Product is "safer" than another (unless endorsed and/or required by regulatory authorities	For CT, please refer to answer n°1 to comment n°1. The sentence on the application of the PP has been re-phrased (not mentioning PP) to avoid misinterpretations about risk management and inconsistencies with TPD.

83.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.2.3 Evaluation	After conclusion of Step 2, it is not yet possible to determine whether an additive increases the toxic or addictive effects or the CMR properties at the stage of consumption to a significant or measurable degree as required by Art. 7(9) TPD. In particular, it is not correct that "if it is demonstrated that compounds proven to have CMR properties are generated from pyrolysis of an additive, this additive will not meet the TPD requirement" (p. 23, l. 23-25). Just based on the compounds generated from pyrolysis of an additive, it is not possible to determine if the additive increases the CMR properties of the whole tobacco products at the stage of consumption and, if yes, whether the increase is to a significant or measurable degree, which is a necessary assessment under Art. 6 and 7 TPD. This requires comparative testing (see in more detail section 2.4.3.1). Therefore, we recommend to replace the whole paragraph "Again, (…) Step 3." (p. 23, l. 20-28) with "After evaluating the pyrolysis products, testing should proceed with Step 3."	Please see the answer to comment 1. The text has been re-phrased to avoid misinterpretations about risk management, but the meaning has not changed.
84.	Thielen, Anja, Deutscher Zigarettenverband DZV, a.thielen@zigarettenverband.de, Germany	2.4.2.3 Evaluation	*Repetition of comment 11*	Please see the answer to comment n°11.
85.	Marshall, Lindsay, Humane Society International, lmarshall@hsi	2.4.2.3 Evaluation	We would partly accept implementation of step 2, in that this proposes to use literature to identify pyrolysis products. However, although there may be some requirement for experimentation in this step, the opinion only states that these experiments should exclude in vivo or in vitro studies. We	There is no need for in vivo studies for pyrolysis studies, being only chemical/analytical experiments for the identification of pyrolysis products (on which the available data are then collected).

	.org, United Kingdom		propose that implementation of Step 2 does not require in vivo studies, for many reasons. Analysis of pyrolysis products from tobacco was first carried out in 1957 (Lam, 1957) and methods to do this are now relatively routine, using standard mass spectrometry and gas chromatography techniques (e.g.,Regueiro et al., 2016 and Paschke 2016); therefore employing equipment routinely found in analytical labs and permitting sophisticated analysis without any in vivo experimentation.	
86.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.2.3 Evaluation	*Repetition of comment 11*	Please see the answer to comment n°11.
87.	Marshall, Lindsay , Humane Society International, lmarshall@hsi.org, United Kingdom	2.4.2.3 Evaluation	Further, in Step 2, for evaluation (p23, lines 25 and 26), the opinion states that "when case data are unavailable, insufficient or not robust enough to make any evaluation possible, the procedure should go to Step 3". We disagree. Step 3 requires further testing and may involve in vivo tests, indeed it is likely to require in vivo testing to evaluate carcinogenic, mutagenic or toxic for reproduction (CMR) potential. Given the nature of these products and the lack of any health benefit from their development, we would suggest that products that lack sufficient data which therefore meet the definition provided "when case data are unavailable, insufficient or not robust enough to make any evaluation possible" do not meet Tobacco Product Directive (TPD)requirements and should go no further. Smoking is a leading cause of	The text has been re-phrased to avoid misinterpretations. The SCHEER considers it questionable to ask for new in vivo studies in Step 3. Only in vivo studies that are already available are taken into account. Only exceptional cases for in vivo study are foreseen, which should be agreed before starting with the Competent authority.

			preventable disease and the public health risks and costs are well- documented. There is an extensive body of knowledge characterising the hazardous components of tobacco smoke and these hazards are unlikely to be reduced with the addition of any of the additives in question. We strongly suggest that any cases with unavailable evidence or insufficient data are not evaluated any further and definitely do not move into in vivo testing in any capacity.	

88.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.3 Step 3: Testing and evaluation of results	The Opinion emphasises that "The outcomes of tests must be related to actual human exposure and tobacco-induced diseases" {p.23:30-33}, but does not provide a validated alternative to comparative testing which satisfies these criteria. The Opinion also states that "this step will also address the possible interactions at chemical level (e.g. pyrolysis) for the toxicological part…" However, unless a relevant tobacco matrix is included in the pyrolysis conditions, such interactions would not be able to be measured and would only be able to be hypothetically postulated, which would be inappropriate in a comprehensive study of this nature – particularly when an approach is readily available that would allow measurement of such reactions in a real-life simulation. The Opinion fails to provide comprehensive guidance on the testing requirements; "toxicity" testing is too broad, and, for example, the relevance of a skin sensitisation assay on an additive present at only a few parts per million should be challenged if the same ingredient is already being used in shampoos, and no concerns have been raised over its sensitising potential in this context. Article 6 TPD2 also explicitly states that "studies shall take into account the intended use of the products". Skin sensitisation does not consider the intended use of combustible tobacco products.	Please see the answer on comment 1, regarding comparative testing. Regarding pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). From the ToR: *The Committee is asked to advise the Commission on the type and criteria for comprehensive studies that should be requested from manufacturers to assess the relevance of the individual additives,….* The SCHEER was not therefore asked to provide detailed protocols. Considering the nature of the products some test can be relevant or not. As for any other regulatory area, it is possible that whenever there is a good scientifically based and acceptable reason for a derogation to present data for a specific end-point, a justification can be provided (exactly as for any other regulatory requests). This is clarified in the revised version in the appropriate sub-chapter (page 24).
89.	Simms, Liam, Imperial Tobacco Limited, liam.simms@ uk.imptob.co m, United	2.4.3 Step 3: Testing and evaluation of results	Page 23, Line 30: It is unclear why SCHEER feels pyrolysis is a viable method when it is known that the use of pyrolysis studies to predict the formation of potentially hazardous chemicals from additives is unreliable (Baker et al., 2004; Purkis et al., 2011; Baker et	Please see the answer to comment 72.

	Kingdom		al., 2005; Stotesbury et al., 1979). In 2013, the German Institute for Standardization (DIN) stated that "Substances generated by pyrolysis are not necessarily identical with those obtained by combustion within the tobacco matrix". Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. It is unrealistic to consider all of the pyrolysis products of an individual additive, as the experimental pyrolysis process is not representative of the combustion process within a cigarette. Instead, we recommend a comparison of smoke chemistry from products with and without the additive included. Here, we recommend the use of comparative smoke chemistry and biological smoke testing of cigarettes in human relevant assays, as the most comparative to conditions of use and consumer exposure. Art. 6.2(a) the Directive states "…effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.". It is the sole responsibility of manufacturers/importers to carry out comprehensive studies, to do so effectively, requires a combination of biological end points within a systematic weight of evidence approach.	For CT, please refer to answer n°1 to comment n°1. Please see the answer on comment 1, regarding comparative testing. Regarding pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products"). For CT, please see the answer n°1 to comment n°1. The application of WoE approach is already addressed in the preliminary Opinion.

90.	*No agreement to disclose personal data*	2.4.3 Step 3: Testing and evaluation of results	For the assessment of priority ingredients SCHEER suggest extensive and comprehensive studies. A varity of these methods were developed over years in an academical environment and such methods are very time consuming. At the same time it is expected from the tobacco industry to develop new methods for evaluation within a time period of 18 months. The requirements are far beyond what the most companies and authorities can handle.	The SCHEER disagree with this interpretation. The SCHEER considers the time frame feasible, also in view of some comments sent by TI in which it is stated that before using an additive TI carries out testing to evaluate its safety both as a single chemical as well as in comparative testing: therefore TI should not be worried, since most of the data indicated in the step procedure described in the Opinion are available. As clearly stated in step 1 and step 2, all the available data should be presented. In case they are sufficient for the evaluation, no testing is needed (no step 3 activity). The SCHEER is not asking companies to develop any new methods in 18 months.
91.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3 Step 3: Testing and evaluation of results	We suggest replacing "attractiveness" (p. 23, l. 37 and l. 39) with "characterizing flavor" since attractiveness is not a relevant criterion under Art. 6 and 7 TPD.	The suggestion has been accepted and the text has been changed accordingly.
92.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United Kingdom	2.4.3.1 Comparative paradigms are not endorsed	SCHEER discounts comparative testing ("CT") on the grounds that "Due to the high intrinsic toxicity of tobacco products, it is challenging to demonstrate any differences, whether they be increases or decreases, induced by an additive." {p.24:12-14}. However, this is precisely the reason that additives should be tested within a tobacco matrix. Art 6(3) TPD2 requires studies to "take into account the intended use of the products concerned." Testing the pure additive would distort the results, as they would not be representative of the effects of additives on tobacco products, and would preclude us from complying with our obligations under Art 6. CT is necessary to fully comply with Art6, para. 2, which, requires assessment of whether additives contribute to or increase "the toxicity or addictiveness of any of the products concerned to a	For CT, please see the answer n°1 to comment n°1.

			significant or measurable degree". The most appropriate way to test a burnt tobacco additive, and hence its breakdown products, is under conditions of use (in a cigarette). This takes account of interactions between compounds, possible additive effects and the impact of complex mixtures. The examination of whether an additive results in a characterising flavour equally presupposes CT to assess to what degree the additive affects the flavour of the cigarettes or RYO. It would likewise be impossible to examine whether an additive "facilitates" inhalation or nicotine uptake without CT. Finally, CT is also required to assess whether the use of the additives "has the effect of increasing CMR properties." In short, without CT it is unlikely that the "comprehensive studies" would comply with the requirements of Art6. The Opinion cites Oldham et al as supporting the claim that CT is inappropriate (p.24:18). However, this neglects the paper's finding that "Comparative toxicity studies carried out for the toxicological assessment of cigarette ingredients demonstrate reliable interstudy and inter-laboratory reproducibility. In addition, the discriminatory power of these studies is suitable for the detection of differences in the toxicity of MS that may potentially be introduced by the use of ingredients". Moreover, Article 6 para. 2(a) and (d) state that the studies are to ascertain whether the increase is "to a significant or measurable degree." Where there is no such increase, there is no requirement to measure it under Article 6 paras. 2(a) and (d). The Opinion refers to Kienhuis et al., (2016) [11] (p.24:12, 25:2) but fails to note that this paper describes CT as the "only way to assess whether additives increase the overall toxicity of tobacco products, as is required in the new TPD." The paper	There is no contradiction, since the SCHEER agrees that is would be the only way, but unfortunately the currently available methodologies are not sensitive enough for this type of testing. This is also the conclusion of the cited paper. A sentence cannot be taken out of context.

			notes that this is also the approach "proposed by the FDA." It is interesting to note that the Committee rejects this view, but endorses other proposals in the same paper. A number of articles have shown differences in toxicity for products with different levels of ingredients. For example, Scott et al. [12] and Carmines at al. [13] indicate observed changes when an ingredient is added. It is therefore evident that it is not that the tests lack discriminatory power, but that the quantity of additive in question does not significantly affect the composition of the smoke. Non-comparative studies fail to account for pyrosynthesis reactions with reactions in situ, and so results are not comparable to results obtained in a cigarette.	Please see the answer on comment 1, regarding comparative testing. Regarding pyrosynthesis, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products").
93.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.4.3.1 Comparative paradigms are not endorsed	p. 24, l. 6-8. "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. p. 24, l.11–14 Please consider that the weight of evidence based on an overall evaluation of all available information should be considered, before drawing any conclusions regarding the toxicological implications of the addition of a certain additive. Notably, Dempsey et al. 2011 noted that "[t]he conclusions should also include the consideration that the added ingredients displace some portion of	The comment has been accepted and the text has been changed accordingly. The WoE approach was already indicated as the methodology to evaluate data. It was repeated in the revised version, to be used whenever deemed necessary.

			the tobacco. Accordingly, any activity derived from the burned additive should not be larger than the activity obtained from the burned tobacco itself, rather than demanding a completely inert material.”	
			p. 24, l. 15 – 18 Please refer to Scott et al., 2013 who investigated the resolving power of in vitro assays. The author fully characterized each assay documenting the resolving power depending on criteria such as slopes, intercept or common dose. Please note that regulatory guidance for genotoxicity testing using e.g. the Ames assay, MLA or IVMNT (ICH, 1995; OECD, 1997, 2014, 2016) emphasizes the assays biological responses rather reliance on statistical techniques alone. Please note that the OECD stated that ‘‘biological relevance of the results should be considered first. Statistical methods may be used as an aid in evaluating test results. Statistical significance should not be the only determining factor for a positive response’’ (OECD, 1997).	The SCHEER refers to OECD TG already used and adopted for regulatory purposes. All the considerations in the comment are therefore already addressed.
			p.25, l.4 As discussed in the guidance document published by the German Standard Organization DIN, the use of control cigarettes with varying specifications (e.g. tobacco blends) does not seem to be necessary. A literature review revealed that given additives have been tested with variable control cigarettes in several laboratories. Despite the use of different control cigarettes, comparisons between the control and the test cigarettes led to the same results.	If this comment means to say that the toxicity of all different types of cigarettes is the same, this proves the point that the assays used are not sufficiently sensitive, since there are large differences in the chemical composition of cigarettes from different tobacco blends.
			p.25, l.11-13 The discussion related to identifying the appropriate comparator (reference) calls into question the rationale for excluding comparative assessments, i.e., a comparative study would need to be conducted using a blend with no 'natural	Please again see the answer for CT (comment n°1)

			sugars' vs Sugars. p.25, l.18-20 Please mention that sugars are allowed by the TPD2 and should only be banned if they result in a characterizing flavor or increase CMR properties.	
94.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.1 Comparative paradigms are not endorsed	Art. 6.2(a) of the Directive states "…the effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.", and Art. 6.2(d) states "leads to the formation of substances that have CMR properties, the quantities thereof…". These provisions must be viewed relative to reasonable consumer exposure, and under the conditions of use. Page 24, Lines 14-18: Art 6.2(a) the Directive states "…effect of increasing the toxicity or addictiveness of any of the products concerned to a significant or measurable degree.". It is the sole responsibility of manufacturers/importers to carry out comprehensive studies, to do so effectively, requires a combination of biological end points within a systematic weight of evidence approach. Oldham et al., (2012) cites several references which have found differences in histological evaluation of cigarettes both with and without specific additives in rats (with a lower discriminatory power than simpler in vitro assays). This indicates clearly that the assays do have the power to discriminate. Page 24, Lines 21- 23: Tests are currently available and can discriminate differences. Routine assessment of additives, and histopathological changes have been detected between different test cigarettes (Coggins 2011 a,b,c,, Roemer 2010). Differences in the smoke chemistry relating to the addition of 333 additives	For CT, please see the answer n°1 to comment n°1 The SCHEER agrees that in some cases, differences have been reported. Still, with CT, due to the lack of discrimination, in almost all of the cases, the conclusion will be that there is **no measurable increase**. In that case, all testing will be meaningless. For instance, in the example concerning sugar combustion provided below, in which more than 10% sugars are added, no differences have been found. However, if this amount of sugar is combusted, this will result in large quantities of toxic and carcinogenic pyrolysis products.

			was seen with both higher and lower levels of specific chemical analytes, however histological changes were not seen during subsequent inhalation studies (Carmines et al., 2002). We therefore believe the use of pre-existing industry data is suitable for usage and should not be ignored by SCHEER. Page 24, Lines 38- 44: Differences in toxicity, and other differences can be detected in current assays used by the tobacco industry. The current Industry approach uses an enhanced approach with Ames (Kilford et al., 2014) and IVM assays, to test the biological activity. Page 25, Lines 4-10: Art. 6.3 of the Directive states "….studies shall take into account the intended use of the products….". This hypothesis is not representative under the conditions required for the intended use of tobacco products and therefore falls short of the mandate. Page 25, Lines 18- 20: No biological in vivo or in vitro effect of sugars have been observed when added up to 10.5% by weight on the cigarette when compared to reference products (Gaworski et al., 1999; Baker et al., 2004, Roemer et al., 2010). Coggins et al., 2011d. reported that the addition of high fructose corn syrup to cigarettes led to a reduced goblet cell activity in the trachea and reduced hyperplasia /metaplasia of the mid vocal chords region when compared the reference product without additives (Coggins 2011d). Page 25, Lines 23-25: No validated studies exist for the determination of pyrolysis products from tobacco additives.	Please see the answer on comment 1. Strictly speaking, the comment provided only proves that additives are as toxic as tobacco. Otherwise, cigarettes with additives would be less harmful than cigarettes without additives. Please also refer to our general answer on comparative testing.

			Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. In seeking a pragmatic and efficient approach to additive assessment, we support a weight of evidence approach which includes reference to comparative toxicology. Not only would this system utilize a combination of existing data, reducing the weight of testing, it would also include the use of validated and accepted protocols such as those of the OECD. EFSA (2013) recommend using chemical mixture data where it is available, with cigarette smoke cited as a classic complex mixture. One constituent in isolation clearly does not provide an overview of the complex mixture as a whole, or accurately represent what smokers are actually exposed to.	Please see the replies to the previous comments on pyrolysis, such as n°72. The WoE approach was already endorsed by the SCHEER in the Preliminary Opinion. Therefore there is no disagreement. Please see the answer to comment 1.
95.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.1 Comparative paradigms are not endorsed	As already stated in our comment to the Abstract, Art. 7(9) TPD sets as relevant criteria whether the additive at study "increase(s) the toxic or addictive effect, or the CMR properties of a tobacco product at the stage of consumption". Therefore, it is not in line with Art. 7(9) TPD to consider only "the effects of the pure additive, and its pyrolysis products" (p. 25, l. 23-24) as proposed by DKFZ and endorsed by SCHEER. Instead, it is necessary to conduct comparative tests. Notably, the view that the TPD requires comparative testing is also shared by the National Institute for Public Health and the Environment's (RIVM's) researchers but not yet reflected in opinion 2: "Comparative testing is the only way to assess whether additives increase the overall toxicity of	For CT, please refer to answer n°1 to comment n°1. There is no contradiction, since the SCHEER agrees that is would be the only way, but unfortunately the currently available methodologies are not sensitive enough to suffice for this type of testing. This is the conclusion also of the cited paper. A sentence cannot be taken out of context.

			tobacco products, as is required in the new TPD" (Kienhuis et al., 2016, p. 99). Comparative testing is recommended by DIN 10133 (2014): "For a 'practical' evaluation to be as realistic as possible, the assessment of the toxicity of an additive only makes sense when cigarettes with the additive under test are compared to identical cigarettes without the additive" (DIN 2014, p. 10). Comparative testing is also consistent with the approach recommended by the Institute of Medicine, which recommended that cigarette additives be reviewed "with the objective of identifying those ingredients that add no significant toxicity to tobacco products and therefore can be considered safe in the context of this use" (Institute of Medicine, 2001). Comparative testing strategies should not be dismissed just because of doubts whether the tests have sufficient discriminatory power to detect increases in toxicity caused by additives. While none of the sources cited in opinion 2 claims that comparative testing lacks discriminatory power but just raise doubts, one of the cited sources confirms that comparative testing has sufficient discriminatory power: "In addition, the discriminatory power of these studies is suitable for the detection of differences in the toxicity of mainstream cigarette smoke that may potentially be introduced by use of ingredients. […] For the overall assessment of cigarette ingredients or any other test item, a weight-of-the-evidence (consideration of all data) evaluation by experienced researchers balancing the strengths and weaknesses of the various levels of complexity and biological relevance in a tiered battery of complementary test systems is required" (Oldham et al., p. 59 – 60).	

			However, if SCHEER still has concerns that existing tests lack sufficient discriminatory power, we encourage SCHEER to trigger the development of relevant research and would welcome any opportunity to contribute to this research and method development. Today, we believe that there is no other way forward since comparative testing is required by Art. 6(2), (3) and Art. 7(9) TPD. Neither should comparative testing be dismissed because testing can only be performed on a product-by-product basis (p. 25, l. 4-10). A large number of published studies have shown that the result of such comparative tests do not depend upon the tobacco matrix of a specific product (see references uploaded in this section). We propose to use the DIN concept of "principle-based" assay which has the advantage that additives are tested at various concentrations including elevated concentrations which are higher than the actual concentration used in reality, which carries the added benefit of enabling the possibility to set, if relevant, maximum content levels for an additive, as provided by Art. 7(11) TPD. Therefore, we suggest amending the whole section 2.4.3.1 to reflect that comparative testing is necessary.	Reporting on research need was not included in the SCHEER ToR, however, it is clear that whenever the SCHEER stated that no validated studies exist for a certain end-point, a potential for a relevant research is highlighted. A paragraph was included at the end of chapter 4. The SCHEER reiterated the rationale that the results of comparative toxicity testing strategies, where differences in the effect of the tobacco product with and without the additive are evaluated, cannot be generalised to all products and brands, having a different composition with respect to tobacco type, blend and additives.
96.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.3.1 Comparative paradigms are not endorsed	We agree with SCHEER's recommendation to use in silico and in vitro based methods for data gaps; however, we suggest that results from these tests are considered together using a 'weight of evidence' approach. For example, we recommend drawing on the comprehensive data sets available for many additives due to their widespread use as a food or healthcare components. This recommendation is	The WoE approach was already endorsed by the SCHEER in the preliminary Opinion. Therefore there is no disagreement. It was further clarified in the revised version.

			made due to the relative high false-positive predictions of in silico/vitro techniques (Serafimova et al., 2010). We agree with SCHEER on the avoidance of animal and human studies, but add that where such studies have been completed the data is utilised where scientifically relevant. We do not commission or conduct research involving animals, and would not undertake such research unless formally required to do so by governments or by recognised regulatory authorities. We agree with SCHEER on the avoidance of animal and human studies, but add that where such studies have been completed the data is utilised where scientifically relevant.	The comment has been accepted and the text has been clarified. The suggestion has been accepted and the text has been clarified.
97.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.4.3.1 Comparative paradigms are not endorsed	The assessment of tobacco additives under combustion and pyrolysis conditions without using tobacco shall not be recommended. SCHEER suggests that comparative studies are not endorsed due to the lack of discriminative power and inability of generalization from one specific testing blend to others. This guidance contradicts the relevant provisions of TPD2. As noted above, Article 6(2)(a) and (d) require the assessment of toxicity, addictiveness and CMR properties by reference to the relevant products and, on a similar basis, Article 7(9) only bans additives that increase the toxicity, addictiveness or CMR effect of the product as a whole. Therefore, it is unclear how data that only relates to combustion of the additive in isolation would, of itself, further the purpose envisaged by TPD2. The SCHEER argues that comparative studies are	See our answer to comment n° 72. For CT, please refer to answer n°1 to comment n°1.

			inappropriate because they render "subtle differences" in toxicity or other properties similar unnoticeable and asserts that, given the "highly toxic" nature of tobacco smoke, this approach requires "very sensitive" tests. This also appears to be based on the fundamental misinterpretation of TPD2. In making these criticisms of comparative studies, the SCHEER, rather than accept that Article 6(2) is intended to ascertain when an additive produces an impact that is measureable upon consumption of the final product, so that the prohibition in Article 7(9) can then be invoked, it instead adopts a methodology that obscures this and is inconsistent with TPD2. Hence, the criteria/evaluation (to ban an additive if any CMRs occur in pyrolysates) proposed by SCHEER cannot be endorsed as a pure additive pyrolysis study represents simply a model study to estimate possible smoke constituents in cigarette mainstream smoke but far from the actual conditions. As SCHEER noted, "Most importantly, the test outcomes should be relevant for tobacco smoking". Thus, SCHEER should not suggest that absolute criteria (Step 2 – test proposal) and should endorse the comparative testing to assess the effect of each additive and their pyrolysates under the actual condition of use. The guidance provided by SCHEER is inconsistent with the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon	

			consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation. Another publication in which one of the external experts of SCHEER acts as co-author concludes that "comparative testing is the only way to assess whether additives increase the overall toxicity of tobacco products, as is required in the new TPD." [Kienhuis, A.S., Soeteman-Hernández, L.G., Staal, Y.C.M., van de Nobelen, S., Talhout, R., A test strategy for the assessment of additive attributed toxicity of tobacco products, Food and Chemical Toxicology (2016), doi: 10.1016/j.fct.2016.05.002.: 4. Discussion and Recommendations for Regulation 2) "To compare the toxic potential of tobacco products with the additive to the toxic potential of tobacco products without the additive by comparative testing. Comparative testing is the only way to assess whether additives increase the overall toxicity of tobacco products, as is required in the new TPD."]	There is no contradiction, since the SCHEER agrees that is would be the only way, but unfortunately testing with the currently available methodologies is not sensitive enough. This is also the conclusion of the cited paper. A sentence cannot be taken out of context.
98.	Bosse, Andrea, DVAI - German Association of the Flavour Industry, info@dvai-dvrh.eu, Germany	2.4.3.1 Comparative paradigms are not endorsed	The SCHEER opinion states that comparative paradigms between products with or without the additive are not endorsed because of a lack of discriminatory power. The methods that are recommended by the DIN SPEC 10133 and by CORESTA [1] are based on comparative studies and provide enough sensitivity to show a possible negative effect of an additive. Kienhuis et al. 2016 conclude that "comparative testing is the only way to assess whether additives increase the overall toxicity of tobacco products, as is required in the new TPD." [2] [1]CORESTA In Vitro Toxicity Testing of Tobacco Smoke Task Force: The Rationale and Strategy for	For CT, please refer to answer n°1 to comment n°1. There is no contradiction, since the SCHEER agrees that is would be the only way, but unfortunately the currently available methodologies are not sensitive enough for adequate testing. This is the conclusion also of the cited paper. A sentence cannot be taken out of context.

			Conducting In Vitro Toxicology of Tobacco Smoke (May 2004). Available at: https://www.coresta.org/sites/default/files/technical_documents/main/IVT_TF_Rationale-IVT-Testing-Tob.-Smoke_Report_Jun04.pdf [2] Kienhuis, A.S., Soeteman-Hernández, L.G., Staal, Y.C.M., van de Nobelen, S., Talhout, R., A test strategy for the assessment of additive attributed toxicity of tobacco products, Food and Chemical Toxicology (2016), doi: 10.1016/j.fct.2016.05.002.: 4. Discussion and Recommendations for Regulation 2) "To compare the toxic potential of tobacco products with the additive to the toxic potential of tobacco products without the additive by comparative testing. Comparative testing is the only way to assess whether additives increase the overall toxicity of tobacco products, as is required in the new TPD."	
99.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.2 The use of animal testing	*Repetition of comment Nr 96*	Please see the answer to comment n°96.
100.	Curren, Rodger, Institute fro In Vitro Sciences, Inc., rcurren@iivs.org, Other	2.4.3.2 The use of animal testing	In general, comments are to lines 27-41 of 2.4.3.2 The SCHEER report makes a powerful contribution to the overall science of assessing tobacco additives by stating that "…as a principle, only in silico and in vitro studies will be considered …" Although the report makes this statement based solely on ethical concerns, it is also justified for scientific considerations, i.e. nearly all existing animal models for inhalation toxicity have little relationship to	Thank you for the positive comment.

			human exposures and responses to tobacco products. For example, a recent U.S. report (IOM [Institute of Medicine]. 2013. Scientific Standards for Studies on Modified Risk Tobacco Products. Washington, DC: The National Academies Press) states, "While it is informative to observe the effects of tobacco products in live animal models, it is not possible to mimic human use patterns of combusted products in laboratory animals. This necessary introduces some artificiality to the experiments, and limits meaningful extrapolation of the findings from animal models to human effects." The SCHEER report further proposes an alternative process, suggesting "a testing strategy including in silico, in vitro and only in exceptional cases in vivo tests." We at the Institute for in Vitro Sciences strongly support this approach, and believe that as three-dimensional human cell models of the human respiratory tract (and the ability to connect these to other human organ models) continue to mature, they will provide far better predictions of potential risk to humans than any animal model can hope to accomplish.	
101.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.3.2 The use of animal testing	The use of animal testing on voluntary products is at odds with the European Union's objective to promote animal welfare (Article 13 TFEU) and to replace, reduce and refine animal testing (Directive 2010/63/EU). BAT does not endorse the use of further animal testing, but considers that past studies may be used in order to apply read-across techniques to identify likely outcomes. In the context of addictiveness tests, the administration of any isolated additives in animals is not relevant to tobacco smoking, since an additive would never be a sole exposure agent; the effects of the additive must be examined in the correct	This is also the SCHEER position. Collection of all the available data in Step 1 and 2 included also the available studies on animal models. The SCHEER was not considering new in vivo studies in Step 3. This has been further clarified in the revised version. Please see the answer to comment n°1. .

			context, i.e. in a smoke mixture along with all the other smoke constituents. Individual chemicals in smoke may enhance or depress addictiveness potential and as such an individual chemical must be examined with all the other chemicals to assess the true overall response. The other issue is that additives are not administered relative to blood levels seen in actual smokers. Some published studies have used rat models and injected chemicals co-found in cigarette smoke at the levels they are present in smoke and not at levels that are found in human blood while cigarette smoking. Chemicals in smoke enter the bloodstream, as well as the brain, to differing degrees and the presence of a chemical in inhaled smoke is not an indicator of how much will remain in the human body during smoking. Some chemicals, e.g. formaldehyde, are in smoke at high levels but not retained at all and therefore found only at extremely low levels in the blood of smokers [64]. Conversely, nicotine is almost totally retained [65]. Animal studies do not accurately reflect this.	
102.	Stoddart, Gilly, PETA International Science Consortium Ltd., GillyS@piscltd.org.uk, United Kingdom	2.4.3.2 The use of animal testing	Appropriately, this section emphasizes the ethical concerns regarding the use of animal studies to evaluate tobacco additives as constituents of "voluntary" products. Beginning at line 37, early consultations are recommended to present testing strategies that may include in vivo tests only in "exceptional cases". As noted in our comments to section 2.4, PISC urges the Committee to not endorse animal studies without exception. In the event the Committee allows the possibility of exceptions, it would be helpful to include an example of such an exceptional case in order to illustrate how rarely such cases are expected to	Thank you for the positive comment. Regarding exceptional cases, since the nature of additive can be extremely different, it is not possible to foresee all the possible examples; on the other hand to list only a few of them could be misleading. For this reason, the SCHEER asked that any in vivo study should be discussed prior conduction with the Competent Authority.

			arise.	
103.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.3 Quality system	All methods that inform regulatory measures must be robust, reproducible, and repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology.	The SCHEER has indeed asked to use whenever possible existing toxicological testing standards and assays recognised by bodies such as the OECD. The SCHEER agrees that validated methods should be the best choice; this is the reason why the SCHEER has pointed out the areas in which such validated tests are not available. The use of WoE was already endorsed by the SCHEER. This has been further clarified in the revised version.
104.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.3 Quality system	Since attractiveness is not a relevant criteria under the TPD we suggest to delete "and attractiveness" on p.26, l. 5.	The suggestion has been accepted and the text has been changed accordingly.
105.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United Kingdom	2.4.3.4 Toxicity testing	SCHEER provide links to a good range of the available in silico models, predictive tools and databases. However, the Opinion provides no clear guidance on how to evaluate and interpret model predictions, but states that "predictivity must be assessed case-by-case on the basis of clear documentation", which negates the benefit of a step-wise approach. SCHEER emphasises 'whole aerosol' testing and states that "[t]hese assays may also be used to explore interactions between components of cigarette smoke" (p28, line 36), which reinforces the argument that comparative testing is the most appropriate method and contradicts its position throughout the Opinion that work is needed as understanding of those interactions is scant. SCHEER recommends the use of IATAs; these are	Due to the different applicability domain typical for QSAR models, it is not possible to suggest a single fit for all models. Therefore the SCHEER reiterate that the most appropriate model should be evaluated on a case-by-case basis. The SCHEER does see any link in support of CT.

			currently not in place, and are unlikely to be so in the timelines permitted for the testing of the priority additives. As described by Tollefsen et al (2014) [71], such an approach may not be appropriate for mixtures of chemicals with differing AOPs "This is relatively straightforward for a simple linear AOP with a limited number of KEs, such as that for skin sensitization. As more AOPs are developed, and KEs are identified that cut across different AOPs into networks of interlinked AOPs, the complexity of data integration supporting an IATA will increase." They continue "Going forward, the challenges foreseen will be to identify the data gaps and assay needs, to integrate different AOPs together to provide a more holistic assessment of likely effects. The latter is a major issue as an AOP by its nature assumes that adversity can be described… whereas the question remains of how many AOPs need to be integrated into IATA to assure that there is no important hazard or adversity overlooked." Again, this will be critical for the assessment of complex mixtures such as tobacco smoke.	The SCHEER disagrees. IATA putting together kinetic and dynamic data are endorsed by ECVAM, as well as by OECD. Please refer to the document cited in the preliminary Opinion.
			A number of OECD test guidelines cited on p29:16ff have been deleted from the OECD library as these tests are rarely used and newer tests show a better performance for the same endpoint.[72], namely test guidelines 479 to 482.	The reference is now made to the 2015 OECD guidance document on genetic toxicology testing, rather than listing the TG.
			We question the proposal that in vitro methods to address local toxicity should be performed at the air liquid interface (ALI) for a number of reasons: (1) The relevance of such tests to the use of additives in tobacco products and how this relates to the requirements of TPD2; (2) many of these assays have no degree of quantification; (3) no guidelines govern the use of such assays at the ALI.	It is now clearly stated (page 24) that: *It should be noted that whenever there is a good scientifically based reason for a derogation to present data for a specific end-point, a detailed justification reporting the rationale for the derogation can be provided.* However it should be noted that the use of irritant additives could be problematic. The lung-on-a-chip model is a relatively new model to assess effects upon inhalation. The actual term lung-on-a-chip is widely

				used, for a diverse range of models, but mostly referring to airway cells cultures on an air-liquid-interface while introducing mechanical stretching. Other, simpler, models, like 3D airway cultures, could also be considered in this respect. It is important to keep in mind that this is a model for the human situation. Lung-on-a-chip models and 3D cultures are relatively new, but also promising and do not have the ethical disadvantages of animal models. Also for other models your points should be considered: Deposition in the respiratory tract is different for each model. Also, not every model is suitable to test every endpoint. Each model should be considered in light of it possibilities and impossibilities. In vitro models have disadvantages, but they are also promising for assessing initial effects. When doing research, this should be carefully considered.
			SCHEER identifies two cell transformation assays for carcinogenicity, but these currently only have OECD Guidance Documents which would imply that the assays still require further investigation and validation.	This is fully right, but it is exactly the same situation encountered for cosmetic products.
			As described in the Opinion, there is no one in vitro assay which covers the complexity of reproductive and developmental toxicity. However, we question the proposal to carry out oestrogen and androgen binding assays, as they are neither sensitive nor physiologically relevant for non-endocrine disrupting chemicals, and such tests do not address the fact that there are many different mechanisms associated with reproductive toxicity end points.	There is no striking disagreement between the comment and the SCHEER Opinion.
			Many of the methods described in the Opinion are not validated, e.g. CULTEX, ALI and 3-d models, and are no more than research models, without international recognition or approved test	The SCHEER agrees, and this is exactly what was described in the preliminary Opinion.

			guidelines. Finally, the statement that "…the choice of the test battery should not be fixed a priori, and should be rather tailored on the basis of information coming from the in silico and read-across analysis", seems at odds with the mandate of the Committee to provide advice "to the Commission on the type and criteria for comprehensive studies."	Due to the very different nature of the different additive, and based on the available study, this seems to be the most scientifically acceptable although pragmatic approach to be taken.
106.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.4.3.4 Toxicity testing	p. 26, l.35-39. Please note that as many of the priority additives are natural substances, QSAR would have limited applicability. Additionally, model reliability is a relative concept and is depending on the context in which the model is applied According to current ECHA guidance documentation, the fact that a substance may be indicated as "Suspected mutagen" by QSAR does not mean that ECHA automatically considers it as a classified mutagen. Indeed, all evidence should be taken into account before concluding on the need for a classification and as such, a level of caution should be applied when interpreting output from QSAR models, ECHA, 2016. p. 28, l. 27-30 Contrary to the SCHEER statement, the TTC concept is applicable for inhalation exposures. (see e.g., Drew and Frangos 2007, Carthew et al. 2009, Escher et al. 2010, 2013 and Costigan and Meredith 2015.) p. 30, l. 1-5 Please note that reproductive toxicity is the study of the 'adverse effects [of chemicals] on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring'. Currently, there are no alternative in vitro testing strategies that are accepted to replace the need for animal testing for this toxicity endpoint. In contrast to other toxicity endpoints,	QSAR as well as read across are a possibility, not an obligation. The SCHEER agrees with ECHA approach: indeed application of WoE to all the available data (Form Step 1 and 2, and if not robust enough step 3) is recommended. The comment has been accepted and the text has been changed accordingly. Please note that TTC for inhalation was proposed in papers published in scientific journal but never endorsed in any regulatory context. The SCHEER agrees that at the moment there is no in vitro testing, replacing animal models for reproductive toxicity, and this is clearly addressed in the preliminary Opinion. However, indication can be derived from available in vivo studies (Step 1), also using the oral route, which combined with kinetic information on the possibility of route to route extrapolation, the application of PBPK modelling, read across etc.. can be the basis for a WoE evaluation also for this end-point.

			the possibility to use (Q)SAR models for the prediction of reproductive toxicity is limited. This limitation is due to the complexity of processes involved in both the fertility and developmental processes and as such, this complexity is difficult to predict with computational tools.	
			p. 30, l. 15 Please note that all cell lines have advantages as well as disadvantages. The proposed HepRG cell line is e.g., derived from liver tissue and therefore of limited relevance for the assessment of toxicants that are inhaled. One disadvantage in using primary cell lines are the difficulties encountered when culturing as well as ensuring an appropriate level of reproducibility.	The SCHEER disagrees with some statements: liver cells are relevant, since after absorption (including via inhalation), the liver is the main site of metabolism in which toxic compounds may be formed. The use of primary cell lines can account for the variability among different individuals therefore the differences in the obtained data is not a question of scant reproducibility, but reflect the inter-individual variability (that in some cases means differences in susceptibility to toxic effects).
			p. 30, l. 28-31 Please note that currently, no standardized methods have been validated for this purpose. In vitro exposure systems are currently non-standardized with varying exposure systems, testing methods and sensitivity. (Li et al. 2016). It should also be noted that the use of these methods have also been associated with a loss of particulate matter within the exposure system.	There is no disagreement. The SCHEER also stated that in many areas no validated tests are available.
			p. 31, l. 26-29 Please note that toxicological testing of tobacco products have typically been conducted with the most responsive 'phase' of the tobacco smoke i.e. particulate phase (PP) or Gas vapor (GVP) phase as described in Health Canada Official Method T-501, T-502, and T-503	The suggestion has been accepted and the text has been changed accordingly.
			p. 31, l. 30-33 Currently, there are no defined regulatory protocols for tobacco whole smoke exposure systems, but product testing protocols for assays such as Ames bacterial mutagenicity and Neutral Red Uptake (NRU) cytotoxicity are being developed to support in vitro toxicity testing and	The suggested reference has been added to the revised version of the Opinion.

			disease model development. (Adamson et al., 2014) p. 31, l.46-48 It is confusing that SCHEER seeks to endorse a system to measure quantitative differences, knowing that this current system has no recognized approach to the measurement of dose. p. 32, l.2-4 The admission that the current systems require characterization and validation is evidence enough that these tools are not appropriate.	The SCHEER reported the merging and promising methodologies, without hiding that they are not yet adopted as official methods or guidelines, accepted at regulatory levels.
107.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.4 Toxicity testing	Page 26, Lines 14 to 19: All methods that inform regulatory measures must be robust, reproducible, repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology as well as the use of appropriate in vitro and in silico studies. If in silico data or read-across data produces an in silico alert for CMR, a weight of evidence approach should be used comparing in vitro and any available animal testing data to determine whether an additive has CMR properties or not. An in silico alert for CMR alone, would not be sufficient to determine a CMR, due to the relative high false-positive predictions of in silico techniques (Serafimova et al., 2010). Additionally, the OECD (2010) states that the person providing the "…scientific judgment must have expertise concerning the relevant endpoint(s) and study methods". We are in agreement with this guidance. Page 26, Lines 40-43: If robust in vitro or in vivo data already exists in the literature, an in silico approach would not be	The SCHEER has indeed asked to use whenever possible existing toxicological testing standards and assays recognised by bodies such as the OECD. The SCHEER agrees that validated methods should be the best choice; this is the reason why the SCHEER has pointed out the areas in which such validated tests are not available. The use of WoE was already endorsed by the SCHEER. This has been further stressed in the revised version of the Opinion. There is no disagreement between the commenter and the SCHEER, who suggested a WoE approach for the evaluation of data coming from Step 1 and 2 first and if not robust enough, combined with results coming from Step 3. Consideration about the expertise of the assessor(s) is valid for any regulatory area and is outside the SCHEER mandate. This is in line with the SCHEER position. If data from step 1 and 2 are robust enough for the evaluation, there is no need to go on to Step 3.

			necessary. It should also be noted that there are six additives on the priority list that would not be able to be subjected to read across or in silico testing, as they are mixtures or natural additives (made up of multiple constituents). Page 29, Lines 16-25: It is not necessary to use all of the nine in vitro mutagenicity and genotoxicity tests listed. EFSA (2011) recommends for its tier 1 genotoxicity testing strategy to use the bacterial reverse mutation assay (OECD TF 471) and the in vitro micronucleus assay (OECD TG 487). This is based on an evaluation of different combinations of in vitro genotoxicity assays by Kirkland et al., (2005). A battery of three assays (Ames, In Vitro Micronucleus and Mouse Lymphoma Assays) had a higher sensitivity but resulted in a decreased specificity than a combination of two tests (Ames and In Vitro Micronucleus) for detecting rodent carcinogens. Mammalian assays, preferably using human cells, are most suitable for genotoxicity testing, due to false positives results observed in rodent cells (Kirkland et al., 2007a). The use of yeast cells would not be necessary if testing with human cell lines due to decreased relevance of yeast cell to humans. Both in the European Cosmetic Toiletry and Perfumery Association (COLIPA) project and at the International Workgroup on Genetic Toxicology workshop, it was recommended to avoid the use of p53-compromised cells but instead to use p53-competent and preferably human cells in in vitro mammalian genotoxicity tests (EFSA, 2011). Page 29, Lines 29 to 31:	The application of read across is a possibility to avoid testing, not an obligation. This is in line with the SCHEER approach, suggesting a battery of tests, consisting of a combination of in vitro genotoxicity tests.

			Imperial Tobacco disagrees with the use of in vitro methods to address eye irritation and phototoxicity as they are not relevant for tobacco additives.	This is not always true (eye irritation could be relevant, when chemicals are present in the cigarette smoke with high eye irritation potential). However, the phrase 'whenever relevant ' has been added. In addition it is possible to present a derogation with a scientifically based justification for it. This is more clearly stated in the revised version (upfront to Step 3 introduction)
108.	Curren, Rodger, Institute for In Vitro Sciences, Inc., rcurren@iivs.org, Other	2.4.3.4 Toxicity testing	The SCHEER report presents a reasonably comprehensive survey of existing *in silico* and *in vitro* tools available to assess genotoxicity, local toxicity, and carcinogenicity. The report also addresses currently available *in vitro* approaches to study multiple effects caused by acute and sub-chronic exposure to whole smoke aerosols. This later area provides the most promise to completely eliminate animal studies from all toxicity assessments of smoke components, including additives. Research is advancing quickly in this area, with new aerosol generators, exposure modules and human in vitro respiratory tract models being reported on almost a quarterly basis. The SCHEER report recognizes this rapid evolution and suggests that "…the test battery should not be fixed *a priori* …" Read-across and *in silico* information should help design the test battery. The development of these new approaches should continue to be supported, and resulting new information should be made easily available both to regulators and to all sections of industry, regardless of size. One example of how this can be accomplished would be through open workshops, such as those organized by our institute, the Institute for In Vitro Sciences. Regulators, industry, animal protection groups and academics actively participated in our 2014 workshop on *in vitro* models for COPD (Behrsing, H, Raabe, H, Manuppello, *et al.* (2016) Assessment of In Vitro COPD Models for Tobacco Regulatory Science:	Thank you for the positive comment.

			Workshop Proceedings, Conclusions and Paths Forward for In Vitro Model Use. ATLA 44:129-166), and our 2016 workshop "In Vitro Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products" sharing information and collaboratively discussing ways forward. It is only through opportunities for open communication among all stakeholders that efficient progress can be made to identify strategies for assessing the risk to consumers from tobacco additives, as well as from tobacco products themselves.	
109.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.4 Toxicity testing	The in silico tools proposed by SCHEER can mainly be used to assess the genotoxic and carcinogenic potential of a neat tobacco additive (e.g., DEREK, MultiCASE, Oncologic, TOPKAT, TIMES and OECD toolbox). Several of the available models are based on the potential for a chemical to react with DNA, and therefore they have been shown to best correlate with Ames test data (Benigni et al., 2010). It is important to note that there are few models which have been designed to predict in vivo genotoxicity, or identify genotoxic mechanisms other than DNA reactivity. Based on this comment, we suggest changing the reference on p. 26, l. 14-15 to "If genotoxic data on the additives are not available or are limited, they can be produced using in silico approaches." Because tobacco smoke exposure data are necessary to perform a proper risk assessment showing a possible increase (or decrease) in toxicity, we suggest to add two chapters: "Smoke chemistry studies" and "Transfer studies" on p. 28, l. 31, thereby reflecting the best currently available methods pending further research. We also suggest that the list of the in vitro	The SCHEER decided not to endorse the proposed change in the text, since QSAR models addressing properties other than genotoxicity are also available, although it is recognised in the Opinion that the ones dealing with DNA reactivity are the most developed ones. Please see replies to the previous comments on the relation between pyrolysis and smoke chemistry (e.g. n° 72). The suggestion has been accepted. To avoid misinterpretations,

			genotoxicity test on p. 29, l. 16-25 be updated based on the new OECD Genetic Toxicology Guidance Document, Guidance Document on Revisions to OECD Genetic Toxicology (2015). Indeed the Test Guidelines (TG) were recently updated and TGs 479, 480, 481, and 482 were officially deleted in 2013. An expert committee decided that "[S]ome tests, for which TGs were developed in the 1980's and 1990's are now considered no longer relevant, or have been replaced by other tests" (OECD, 2015). The resulting updated list is in general agreement with the DIN SPEC 10133 (2014) which listed the following in vitro assays: bacterial reverse mutation assay, DNA micronucleous assay, sister chromatid exchange assay, chromosomal aberration assay, mouse lymphoma assay, neutral red uptake cytotoxicity assay. The DIN regards the following in vitro assay as mandatory: "1) Bacterial mutagenicity; 2) Cytotoxicity in mammalian cells (preferably the Neutral Red Uptake Assay); 3) Genotoxicity in mammalian cells (chromosomal aberration assay or in vitro micronucleus assay)" (DIN SPEC 10133 (2014), p. 27). The list is also in general agreement with Health Canada's "Regulations Amending the Tobacco Reporting Regulations" requiring manufacturers and importers to carry out and report on annual toxicity testing on cigarettes. More specifically, manufacturers and importers are required to perform and report on the following three toxicity tests: Bacterial Reverse Mutation Assay for Mainstream Tobacco Smoke, Neutral Red Uptake Assay for Mainstream Tobacco Smoke and In Vitro Micronucleus Assay for Mainstream Tobacco Smoke. It is not clear in the chapter "In vitro" (p. 28, l. 31) which test substances should be used in the in vitro	the list has been deleted, and the document with the update of genotoxicity strategy by OECD is now cited, advising readers to refer to the most updated one. The agreement extends also to the test of choice for a battery of genotoxicity tests. The comment has been accepted and a clarification has been included in the Opinion.

			tests: the neat additive, cigarette mainstream smoke generated from cigarettes with and without additive(s) or the pyrolysis products of the additive? We kindly ask SCHEER to clarify this. Based on several references to "tobacco smoke condensate", "whole smoke" and "cigarette smoke", we assume that in Step 3 cigarette smoke needs to be investigated and we suggest changing the title of this chapter (p. 28, l. 31) to "In vitro tests with mainstream cigarette smoke". If the pyrolysis products of the additive should be investigated in vitro, methods have yet to be fully developed and validated.	The SCHEER deems unnecessary to change the title of the chapter. In vitro testing refers also to the additive itself, and to pyrolysis products (in many cases they are chemically stable molecules which can be tested with validated methods).
110.	Stoddart, Gilly, PETA International Science Consortium Ltd., GillyS@piscltd.org.uk, United Kingdom	2.4.3.4 Toxicity testing	On page 32, line 18, the cited author's name is spelled incorrectly. The correct spelling is Manuppello. On line 33 of the same page, the web page link for the PETA International Science Consortium Ltd is broken. The correct URL is http://www.piscltd.org.uk/alternatives-approved-by-regulators/.	Thank you for the comment. The typos are now corrected.
111.	mirkova, ekaterina, e.mirkova@gmail.com, Bulgaria	2.4.3.4 Toxicity testing	2.4.3.4 Paragraphs 5&6, page 32  Mirkova_Comments_ TobaccoAdditives_To	Thank you for the advice. This position was in line with the SCHEER Opinion.
112.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva,	2.4.3.5 Addictivenes s testing	p.34,l.31 Please add that no definitive conclusions can be drawn with respect to the functional role related to nAChRs upregulation. (See Le Foll 2016)	The functional role of nAChR upregulation upon tobacco consumption has been repeatedly demonstrated: e.g. when nicotine binds to nAChRs in the brain it mediates a variety of behavioural changes (Lukas 1998), and psychomotor function (Paterson and Nordberg 2000). Nicotine administration also produces reward through DA release in the NAc, at least in part through stimulation of nAChRs in the VTA (Blaha et al. 1996;

	Switzerland, Javier.Martinez@jti.com, Other			Corrigall et al. 1994; Nisell et al. 1994; Yeomans and Baptista 1997; Yoshida et al. 1993) (see Sharma and Brody, 2009). The α4β2* nAChRs mediate many behaviours related to nicotine addiction and are the primary targets for currently approved smoking cessation agents. Moreover, mice in which expression of α5 or β4 subunits has been genetically modified have profoundly altered patterns of nicotine consumption. (see review Picciotto and Kenny, 2013) The conclusion of the article of Foll, 2016 is that short access to nicotine by use of a self-administration model in animals:" intermittent nicotine exposure is sufficient to produce change in nAChRs expression. ….This research suggests that this upregulation may be associated with the early development of nicotine addiction." Therefore, there are strong indications for a functional role of nAChR upregulation in the nicotine reward system even after short periods of exposure.
			p.34,l.35 Statement: "…nicotine reward / addiction mechanisms." Please remove "/ addiction."	The word 'addiction' has been removed.
			p.35,l.32-35 Please delete SCHEER's reference to Usmani et al. 2005, which simply reports a significant antitussive effect of theobromine in healthy subjects when compared with placebo. The dose of theobromine used to assess an antitussive effect was 1000 mg. Please add that SCENIHR 2010 report noted "the content of theobromine per cigarette will be too low to have a bronchodilating effect on the lungs and thereby increase the absorption of nicotine." This allegation is unsupported and should be removed.	Although these concentrations are higher that the theobromine in a single tobacco product, theobromine can have a local anaestatic effect and bronchodilating properties. Therefore the example of theobromine remains as it is now. In addition, the SCHENIHR statement referred to was not given correctly: the SCHEER states: "Regarding addictiveness, several pharmacological effects of cocoa-derived ingredients were reported, including the bronchodilatory effect of theobromine and caffeine, which result in improved bioavailability of nicotine, although data available so far indicate that

				the content of theobromine per cigarette seems to be too low to have a bronchodilating effect on the lungs" (SCENIHR, 2010)
			p.35,l.28-30 Please mention the results generated in the studies by Rose et al. 2010 a,b, that do not support the notion that a correlation exists between the speed of delivery of nicotine and smoking behavior.	The SCHEER mentioned that "inhalation during smoking results in a rapid brain increase of nicotine". The SCHEER does not state anything about a correlation between the speed of delivery and smoking behaviour. Moreover, Rose (2010, Pulmonary delivery of nicotine pyruvate) concludes that: "…inhalations produce rapid increases in plasma nicotine concentrations….." In "Kinetics of brain nicotine accumulation" they suggest that puff-associated spikes in the brain nicotine concentration do not occur during habitual cigarette smoking. Despite the presence of a puff-associated oscillation in the rate of nicotine accumulation, brain nicotine concentration gradually increases during cigarette smoking. These findings underpin the sentence in the manuscript: "It has been shown that inhalation during smoking results in a rapid brain increase of nicotine in the brain".
			p.35,l.35-37 Please add that the SCENIHR 2010 noted that "[t]he particle size of the smoke aerosol does not seem to substantially influence the exposure to nicotine." Furthermore, the SCENIHR concluded that "[b]ased on the limited publicly available information, it seems that exposure to nicotine cannot be substantially increased by altering the particle size of the smoke aerosol."	The sentence does not refer to the particle size of the aerosol in relation to nicotine exposure but to the uptake of the specific particle and the possible effects on nicotine uptake.
			p.36,l.3-5 The notion that higher amounts of uncharged nicotine "will result in more easily absorption of nicotine by epithelial cells in the lungs" is incorrect and should be retracted. The respiratory tract, and particularly the lungs, rapidly	The text has been adapted to reflect the fact that opposing positions on smoke pH and its effect on unprotonated nicotine have been published and studies have been designed in an attempt to evaluate this effect empirically, but not sufficient evidence is available to prove or disprove this point.

			buffers all smoke inhaled to the body's physiological pH of 7.4, irrespective of the "smoke pH" when inhaled, thereby resulting in nicotine absorption at a constant rate. This is definitely supported by the scientific literature, and is not a tobacco industry appanage. The SCENIHR 2010 embraced this evidence as follows: "[…] due to the high buffer capacity of the lining fluid in the lungs it is uncertain if more nicotine is absorbed with higher smoke pH." The current SCHEER working group persistent dismissal (l. 5-9) of this reasoning is inconsistent with the vast majority of the scientific literature and with the SCENIHR 2010 report that concluded that "[a]dditives that reduce the acidity, and thereby the formation of free nicotine, may contribute to addictiveness, but the efficacy of these compounds has not been shown. In view of the buffer capacity of the body fluids involved (saliva, lung lining fluid), the presence of such an effect is doubtful."	
			p.36, l.20-30 Please add that the effect of nicotine clearance on smoking behavior is not completely understood. Please refer to Dr. Benowitz 2009 who elaborated on the notion that slower nicotine metabolites clearance would typically be associated with smoking fewer cigarettes per day, not more.	The SCHEER added a sentence at the beginning of the paragraph: "The metabolism of nicotine is a complex pathway of actions."
			p.40,l.5-7 Please amend: The animal self-administration concept is not widely accepted as "a reliable animal model with high predictive value for the dependence potential of a drug and can be used to support findings observed in humans." Accordingly, SCHHER concedes that animal models "aim to deliver pure nicotine using an intravenous self-administration paradigm despite the fact that nicotine itself is regarded as a relatively weak reinforcer." (p.39, l. 46-47) Please add that most experiments conducted with laboratory animals	The animal self-administration concept is a widely accepted and validated animal model for assessing the dependence potential of many drugs. That the administration of intravenous nicotine as reinforcer is an exposure method which is not comparable and predictable for the effects of exposure during smoking may well be due to the fact that other components in tobacco smoke also play a role in tobacco dependence. This fact does not discredit the self-administration paradigm.

			demonstrate that animals do not voluntarily self-administer nicotine without prior conditioning, which tends to invalidate many such studies. (Dar & Frenk 2004) p.40,l.36-38 Please amend as follows: "[c]ombinations of techniques examining neurochemical physiological and behavioural changes in specific brain regions with nicotine dependence may provide valuable information."	The sentence has been adjusted accordingly.
113.	Simms, Liam, IMperial tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.5 Addictiveness testing	Page 34, Lines 25-27: We agree that there is a lack of validated methods to test additive dependence. All methods that inform regulatory measures must be robust, reproducible, and repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology. Page 35, Lines 6-8: Sugars do not add to the production of acetaldehyde in mainstream smoke on a weight-by-weight basis. Structural components such as cellulose are the primary precursors of acetaldehyde in mainstream smoke (Seeman et al., 2002; Cahours et al., 2012). SCENIHR (2010) demonstrates that during heavy smoking, whilst acetaldehyde in breath rose six-fold in smokers, only minor amounts were absorbed into the blood stream, suggesting no (indirect) addictive effect of sugars when used as a tobacco additive. Page 35, Line 7:	The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Regarding comparative testing, please refer to our answer on comment 1. The SCHEER adapted the sentence to include that there are also other precursors of acetaldehyde in tobacco smoke.

			Acetaldehyde is rapidly metabolised by the body (in seconds) and is produced in large volumes during the metabolism of alcohol. Harmane occurs naturally in many foods including coffee and tobacco. Louis et al., (2011) did not find any relationship between smoking, coffee consumption and harmane blood levels.	The SCHEER agrees that there are other sources of Harman. Still, it can also be formed *in vivo*, via reaction of acetaldehyde with amino acids.
			Page 35, Lines 31-32: The percentage absorption of nicotine from smoking is almost 100%. Changing the form of nicotine, if possible, has little consequence (Greenberg et al., 1952). The theobromine content of cocoa and the amount used in cigarettes is insufficient to have a bronchodilator effect (Mueller et al., .2000, SCENIHR 2010).	The sentence is not about the effect of additives on the form of nicotine, but on the physical properties of smoke: "a change in the physical properties of tobacco (e.g. particle size) can be altered by certain additives to allow (nicotine) particles to enter deeper levels of the lungs (SCENIHR, 2010a)."
			Page 35, Lines 46-47: "Lung on a chip" is not a validated model, with only a limited number of scientific publications.	Although these concentrations are higher that the theobromine in a single tobacco product, theobromine can have a local anaesthetic effect and bronchodilating properties. See also comment 112. "Lung on a chip" is not a validated model, with only a limited number of scientific publications. As this technique is promising and developing quickly, these may be used to further evaluate the exposure to smoking related compounds. The lung-on-a-chip model is a relatively new model to assess effects upon inhalation. The actual term lung-on-a-chip is widely used, for a diverse range of models, but mostly refers to airway cells cultures on an air-liquid-interface while introducing mechanical stretching. Other, simpler, models, like 3D airway cultures, could also be considered in this respect. Although these models are not validated, they can be applied to study toxicity, possibly as one test among other tests.
			Page 36, Lines 1-9: Smoke pH is an artificial measure due to its method of sampling and collection, and is not representative	The SCHEER adapted this sentence, as described in our answer to comment 112.

			of normal smoker exposure. The human body has a high degree of buffering to ensure homeostasis. Changing the form of nicotine in smoke, even if possible will therefore have a negligible effect compared to variable smoking behaviours.	
			Page 36, Lines 23-24: Studies show that inhibition of CYP2A6 leads to a decrease in cigarette consumption and dependence (Tyndale et al., 1999;) with decreased CYP2A6 activity being associated with a decreased cancer risk in smokers in a meta-analysis study (Liu et al 2011).	The statement as described by the reviewer is reflected in the Opinion: Additives modulating the activity of metabolic pathways are therefore likely to affect the dependence potential of nicotine. Furthermore, the SCHEER would like to stress that this paragraph describes the effect on the dependence potential and not on the risk of cancer. Besides that, the association between CYP2A6 and lung cancer is not yet clear. Liu at al. state that the reduced-activity CYP2A6 genotype may decrease the risk of lung cancer in smokers. They also show that they did not find statistically significant relationships between CYP2A6 genotypes and lung cancer in studies that included both never smokers and smokers.
			Page 36, Lines 42-43: The percentage absorption of nicotine from smoking is almost 100%. The hypothesis of changing the ionisation state of nicotine, even if possible, would not have a significant effect on total absorption of nicotine.	It is correct that the percentage absorption of nicotine from smoking is almost 100%. However, absorption is not the most interesting aspect mentioned in this paragraph but it is rather nicotine bioavailability. Bioavailability is defined by an optimal rate of adsorption and distribution from the lungs into the bloodstream.
			Page 37, Line 21: In vivo Positive Emission Tomography scans are research tools used to measure metabolic processes in the body, and priority should be given to hospitals for medical diagnosis.	PET systems are often used outside the medical theatre, e.g. for research purposes.
			Page 38, Lines 47-48: Studying the opioid system does not appear to be a useful method for defining tobacco dependence.	The sentence has been changed accordingly.
			Page 40, Lines 5-7: The self-assessment paradigm is not widely accepted as a reliable animal model (Frenk & Dar	Please see the answer to comment 112.

			2002). SCENIHR in 2010 acknowledged a lack of a suitable animal models adequate for testing addictiveness. Page 40, Lines 36-39: The neurochemistry of the brain is not well understood by scientific experts. The studies outlined by SCHEER will not provide useful information about the addictiveness of tobacco additives as the proposed assays are not validated, contain no methodology and are not readily accessible. The movement of radiolabelled compounds in the brain does not take into account other aspects such as environmental cues and social settings which are traditionally associated with addiction. Page 41, Lines 1-2: To validate an in vitro test for addictiveness within 18 months is unrealistic, as no assays are currently available (SCENIHR 2010).	The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). Furthermore, the SCHEER agrees that environmental cues and social settings are also important in tobacco addiction, but the current Opinion is on the effect of tobacco additives. The SCHEER Opinion does not request the industry to develop a validated test within 18 months. However, all tests performed can contribute to the validation of certain test strategies.
114.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.5 Addictiveness testing	For the 15 selected priority additives, two hypotheses are given in the final SCENIHR Opinion 1 (Table 2) how these additives may impact tobacco smoke addictiveness: cocoa, fenugreek, glycerol, guaiacol, menthol, propylene glycol, and sorbitol are suspected of facilitating inhalation by various mechanisms and cocoa is suspected of also being a MAO inhibitor. We suggest deleting all subsections which are not specifically addressing: facilitating inhalation and MAO inhibition p. 34, l. 31- p. 35, l. 2; p.36, l. 1 - 9; p. 36, l. 20 - 30; p. 37, l. 5 – p. 38, l. 12; p. 38, l. 33 – p. 40, l 32. The in silico method, ligand-based monoamine	The dependence capacity of a compound itself or the contribution to the overall dependency of the product and its underlying mechanisms are not always clear and understood. For the assessment of the potential dependence capacity, a tiered approach is described in this Opinion. This approach will be a guidance to approach all components of the priority list.

			oxidase (MAO) model (p. 35, l. 3), suggested by SCHEER is only indicative and not accurate enough. The approach to combine the in vitro 3D lung-on-a chip with mathematical computer models to investigate nicotine uptake is also not a fit-for-purpose method to "accurately assess tobacco dependence potential for regulatory purposes" (SCHEER p. 40, l. 34). The issue with the latter approach is that modeling of the precise exposure concentration at different regions or airway generations in the respiratory tract is not yet feasible. The difference between the predicted and the measured particle deposition in monkey lungs is huge - a factor of two - as seen in Asgharian et al. (2012) and it is known that the deposition predictability for cigarette smoke is even worse (Robinson et al., 2001; Baker et al, 2006). In addition, the in vitro 3D lung-on-a-chip is a research tools, neither standardized nor validated, and never used to demonstrate if tobacco additives may increase nicotine uptake via mechanisms like bronchodilation, local anaesthetic properties, and changes in pH. Therefore we suggest deleting p. 35, l. 41-47. We would like to ask SCHEER to revise p. 40, l. 41-45. The "recommendations" are too broad and do not give any guidance if manufacturers should perform any tests for the priority list of additives and if so which methods should be performed to "accurately assess tobacco dependence potential for regulatory purposes."	The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke). The lung-on-a-chip model is a relatively new model to assess effects upon inhalation. The actual term lung-on-a-chip is widely used, for a diverse range of models, but mostly referring to airway cells cultures on an air-liquid-interface while introducing mechanical stretching. Other, simpler, models, like 3D airway cultures, could also be considered in this respect. It is important to keep in mind that this is a model for the human situation. Lung-on-a-chip models and 3D cultures are relatively new, but also promising and do not have the ethical disadvantages of animal models. Also for other models your points should be considered: Deposition in the respiratory tract is different for each model. Also, not every model is suitable to test every endpoint. Each model should be considered in light of its possibilities and impossibilities. In vitro models have disadvantages, but they are also promising for assessing initial effects. When doing research, this should be carefully considered. This is outside the remit of the SCHEER mandate. The SCHEER was not asked to give detailed protocols but to advise the Commission on a possible framework to help the MS in asking and Tobacco Industry (TI) to present sound data; in particular the ToR states: *The Committee is asked to advise the Commission on the* ***type and criteria for comprehensive studies*** *that should be requested*. It has been clarified upfront in the text. Regarding the timeframe, the possibility exists that different steps can be run in parallel.
115.	Marshall,	2.4.3.5	Page 36 line 31, lists the in vivo tests that would be	Thank you for this positive comment.

	Lindsay, Humane Society International, lmarshall@hsi.org, United Kingdom	Addictiveness testing	accepted as part of the in vivo, stage 3 testing strategy. We note that these tests are not recommended as first choice and are gratified to see this progressive attitude. However, there are alternatives to all of the in vivo tests that make in vivo testing redundant and we would strongly suggest uptake of the alternatives instead. We note that several Member States (including the UK and Germany) have banned animal testing for tobacco products on the same grounds as the ban on cosmetics testing - these are non-essential luxury products and these new products are similarly non-essential. Thus, these national bans should be extended or applied to non-tobacco cigarette substitutes and novel flavour enhancers/additives.	
116.	Marshall, Lindsay , Humane Society International, lmarshall@hsi.org, United Kingdom	2.4.3.5 Addictiveness testing	Line 32 Biomarkers of nicotine: The analysis of biomarkers may provide powerful data on the effects of additives on the addictiveness of nicotine, but this does not require animal tests. Urine, blood and exhaled breath biomarkers are routinely used to monitor nicotine intake in human smokers. There are sensitive, non-invasive methods for biomarker analysis using relevant human samples that are more informative than animal studies. Human smokers alter their smoking behavior according to cigarette availability (Benowitz et al., 1986), an effect that could never be replicated in animals but that is vital in reflecting accurate exposure and assessing the potential impact of additives. We note that there are increasing numbers of studies recruiting current smokers (D'Ruiz et al., 2016)(Donny et al., 2015) and we see this as an innovation that will provide vital for the studies	Using in vivo animal models for testing the broad range of effects of exposure to non-essential products like tobacco products are not recommended in this tiered approach. The SCHEER agrees that urine, blood and exhaled breath biomarkers can be more valuable and easier to obtain and therefore should be aimed for. In the text, an example of a human study has been provided. For these kind of neuro-imaging experiments, both smokers and non-smokers can be included. The SCHEER agrees that also electroencephalography (EEG) might in the future be used to identify smoking-related behavioural reactions and changes like in

			needed for the Opinion. There are also sophisticated methods available for functional analysis of human craving (Donohue et al., 2016), that could be adapted to examine the influence of additives; an issue which cannot be addressed by animal models.	cravings. This specific EEG paradigm for dissociating the different levels of craving as reported by Donohue et al. is very new and the first reporting on this. Possibly, in the near future more results on the EEG method can be used to define additive-induced dependence.
			Line 44 Dopamine release and turnover: We strongly oppose animal testing on substances designed for human pleasure. These are totally unnecessary and would never enable evaluation of the subjective nature of addiction. To assess the potentially synergistic effects of tobacco additives on dopamine release (addiction) will require human studies with current smokers.	The SCHEER agrees. For ethical reasons, performance of new animal studies is not endorsed to assess the safety of a tobacco additive.
			There are numerous clinical studies that demonstrate methods for the successful measurement of neurotransmitter fluxes in living human brain (e.g., Shingai et al., 2014; Payer et al., 2014;Boileau et al., 2016).Application of these powerful, flexible techniques for live imaging of neurotransmitter release in the human brain to study the effects of additives on addiction would seem to be a better use of resources. This would provide human-relevant data of immediate impact to the Opinion.	The SCHEER agrees on this statement and therefore in vivo human experiments are preferred over animal experiments. Still, human studies are also discouraged; they may be used (e.g. in case of flavour assessment), but only if the study subjects are not exposed to the harmful smoke emissions of tobacco products.
			Page 36 Line 18-19: In vivo MAO activity using PET (see paragraph 18 - neurobiological effects using imaging techniques). Page 37 Paragraph 18 Line 5: Neurobiological effects using imaging techniques.	The SCHEER better indicated the reference to this specific paragraph by adding a page number. The SCHEER removed the '-' and put a '.' instead.
			p. 38, line 13 and 33; Radiotracers for nicotine, nAChreceptors, dopamine receptors, opioid receptors.	The SCHEER changed the heading into Radiotracers and made sub paragraphs with headings for nicotine, nAChreceptors, dopamine receptors and opioid receptors so that the paragraphs are better recognised and traceable.

			For all of the above, we firmly disagree with the use of animals to investigate the effects of additives on the parameters described. Advances in recombinant protein technology, enzyme kinetics and imaging make animal studies entirely redundant (Nag et al., 2016; Shingai et al., 2014; Wing et al., 2015; Payer et al., 2014; Boileau et al., 2016).	The SCHEER agrees, see the statements above.
			Page 39 line 43: Behavioural responses in rodents.	The SCHEER moved the start of the paragraph one sentence lower so that the heading is now above the paragraph itself.
			Studying behavioural responses in rodents provides no insight into the addicted behavior of humans, and never will. We are strongly opposed to the use of animal models for a particularly human act. There are existing, accepted methods to evaluate behavioural response of humans and this Opinion needs to reference these and promote their use.	The SCHEER agrees, see above.
			Page 40 Line 12: Behavioural outcome measures in humans.	The SCHEER moved the start of the paragraph one sentence lower so that the heading is now above the paragraph itself.
			Advances in brain imaging allow sophisticated studies of human neural function under various different states(Feng, 2016). Human studies can make use of the FTND (Fagerstrom Test for Nicotine Dependence) and WISDM (the Wisconsin Inventory for Smoking Dependence Motives) in order to assess smokers' motivation; these questionnaire-based methods are used routinely to inform replacement strategies in encouraging quitting and do not represent an ethical barrier to the use of humans in these studies. These may be adapted to provide a starting point for the analysis of the attractiveness of potential additives. The recruitment and interrogation of current smokers	The SCHEER agree that the use of questionnaires should not be an ethical barrier to use humans in these types of studies. These questionnaires can be adapted to for the assessment of dependence and possibly also for attractiveness of potential additives. The SCHEER added this information in the last sentence of the paragraph.

			has to be an important feature of this Opinion.	
117.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.3.5 Addictiveness testing	The Opinion (PO) claims that the aetiology underlying addictiveness is known but offers no evidence. All cigarettes are addictive, with or without additives; no evidence suggests otherwise.	The SCHEER agrees that all cigarettes are addictive. As there are many substances in tobacco with even more possible mechanisms of action, no clear statement is made in this Opinion about an aetiology underlying addictiveness. Depending on the substance, there might be more than one mechanism involved. Mechanisms with the most conclusive scientific evidence are described in this Opinion.
			Studies show that nicotine in cigarettes is addictive, but smoking-related addiction/dependence (A/D) is a result of a host of complex interactions of chemicals, sensorial cues, neuronal inputs and outputs in different brain regions, cellular processes, molecular events and genetic foundations. Claims that we understand how additives impact these interactions overstate available knowledge and evidence. It is not possible to use any single interaction or cue as a surrogate for quantifying addictiveness; many of the suggested measurements do not take into account this complexity.	Indeed, smoking-related addiction/dependence (A/D) is a result of very complex interactions of chemicals. More information on the mechanisms involved is needed to understand how additives impact these interactions. Therefore, it is of importance to start testing the dependence potential of additives. A special focus should be whether these compounds change nicotine dependence.
			Several methods measure A/D[67, 75, 76, 77]. Clinicians use some to assess smoker dependency and to recommend an intervention. These were refined to examine potential dependence effects of novel tobacco products and e-cigarettes[68]. The PO dismisses them without explanation, claiming limitations due to them 'assessing dependence…not…dependence potential'. But, if something has 'dependence potential' it is likely to cause dependence. Potential cannot be accurately assessed, but dependence can be using tools such as FTCD[67]. SCHEER should re-examine this and measure dependence in humans rather than surrogates that examine only a single, small facet of	The comment has been accepted; the SCHEER added a sentence to this paragraph: However, these questionnaires can be adapted for assessment of dependence to tobacco-related additives.

			it. The PO calls for preclusion of animal and human studies from risk assessment. This is at odds with the objective of examining the effect of additives on inhalation facilitation (IF) which is only possible in a human study. No in vitro or in silico tests can act as a surrogate for a complex behaviour e.g. inhalation, particularly as IF comprises acute responses and long term behavioural adaptations. The proposed use of human lung 3D tissues is not a viable surrogate for inhalation studies, as it precludes input from the behavioural and psychological systems that modulate inhalation patterns. Designing studies relevant to human exposure is so challenging that animal experimentation is not sensible here. Firstly, the issue of how to administer the additive must be addressed. Since an additive is never a sole exposure agent, its effects must be examined in the correct context, i.e. in a smoke mixture with the other smoke constituents. Individual chemicals in smoke may enhance or depress addictiveness potential and as such they must be examined with the others to assess the overall response. The other issue is that an additive along with other smoke chemicals must be administered relative to blood levels in smokers. Studies have injected rats with chemicals at levels present in smoke but not at levels found in smokers' blood. Chemicals enter the bloodstream and the brain to differing degrees; the presence of a chemical in inhaled smoke is not an indicator of how much will remain in the body. Some chemicals, e.g. formaldehyde, are in smoke at high levels but only found at low levels in smokers[64]. Conversely, nicotine is almost wholly retained[65]. Animal studies do not accurately reflect this. The PO	The PO recommends for ethical reasons not to use animal models for the testing of voluntary products like cigarettes. Human studies are considered useful to examine the effects of tobacco additives in dependency or other facets like inhalation facilitation. However, to reduce the cost of experimental testing and the superfluous use of human, the PO describes a step–wise approach in which in vitro and in silico tests are recommended first. The SCHEER agrees that human studies reflect the actual situation more closely than animal experiments. Still, human studies are also discouraged; they may be used (e.g. in case of flavour assessment), but only if the study subjects are not exposed to the harmful smoke emissions of tobacco products. Regarding comparative testing, please refer to our answer on comment 1. For some experiments, current smokers or non-smoking individuals can be exposed to the additive. The SCHEER agrees that no validated tests are available, and therefore, the assessment can be guided by the available knowledge of the mode of action. In the Opinion, the SCHEER provided a short description of the methodologies that can be used. Although for most tobacco additives, direct information about their possible contribution to addictiveness does not exist, information can be derived from the mode of action of the additive (e.g. addictiveness can be related to increased nicotine bioavailability or to local anaesthetic effects facilitating the inhalation of tobacco smoke).

			suggests a number of models for determining addictiveness, including in silico studies of nAChR activation and monoamine oxidase (MAO) inhibition, in vitro models of MAO and CYP enzyme function and in vivo radiotracer/fMRI studies[pg. 34]. There is no consensus on any combination of these tests for regulatory purposes[73], nor any validated link between the outputs of these models and the complex behavioural and psychological response that is addiction. In vitro and animal studies also have limited application in predicting human response to addiction, due to the multitude of contributing factors.	
118.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.3.6 Characterising flavour and inhalation facilitation as contribution to attractiveness	TPD2 defines a characterising flavour as a "clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herb, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product." This is not a clear definition, and relies on subjective terms e.g. "clearly". Sensory diagnostics and chemical-analytical measurements deliver objective results and so subjective terms in the definition must be decoded into measurable objective terms. Furthermore, while sensory diagnostics and chemical measurements produce highly sensitive analytical data they make no sense if they are not validated/calibrated for consumer relevance.	Regarding implementation of characterising flavour assessment, the SCHEER refers to this webpage of the European Commission: http://ec.europa.eu/health/tobacco/products/implementation/characterising_flavours_en.htm
119.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202	2.4.3.6 Characterising flavour and inhalation facilitation as contribution	It is clear that new standardized process are required. Please note that they must take into account contributions from relevant stakeholders and should include a regular review process to ensure that methods are up to date and reflect current knowledge. To comply with the TPD2, this	Regarding implementation of characterising flavour assessment, the SCHEER refers to this webpage of the European Commission: http://ec.europa.eu/health/tobacco/products/implementation/characterising_flavours_en.htm

	Geneva, Switzerland, Javier.Martinez@jti.com, Other	to attractiveness	process must involve a comparison of the subject tobacco product vis-à-vis an appropriate reference. p.42, l.26: "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". The SCHEER precisely points to the only two references to "attractiveness" provided in the TPD2. Tellingly, these references clarify that the industry is not compelled to test for "attractiveness", and highlight the lack of any basis on which the Commission or Member States may take action with respect to "attractive" additives, except in the very limited context of additives that result in a characterizing flavor. Suffice to say, neither the SCHEER nor the Commission has authority to amend the TPD. Consequently, the discussion at pages 42-45 and elsewhere in the Preliminary Opinion regarding "attractiveness" is irrelevant and should be removed. p.43, l. 34-48 + p.44 1-9 The concepts of "harshness and smoothness" and "impact and smoothness "are irrelevant and should be removed, please. Only taste and smell are considered in the definition for characterizing flavor provided by the TPD2. p. 44, l. 2-3 Please amend and add that no scientific data support the claim that the amount of liquorice or menthol in cigarettes permits deeper inhalation, affect smoking inhalation patterns or smoking behavior.	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". Harshness and smoothness are discussed in the context of facilitating inhalation or nicotine uptake, which are described in the TPD2. The SCHEER does not agree: see also the specific sections on liquorice and menthol.

			p. 44, l. 2-6 The statement stating that additives such as liquorice and menthol are used "to make the smoke less aversive and permit deeper inhalation" is pure speculation and should be deleted. None of the studies cited provide any evidence that this occurs. p. 44, l. 10-18 Please note that the term "impact" is inconsistently described as "an industry term for smokers' subjective awareness of the drug effects of nicotine" (l.10-12) and "an industry term denoting the organoleptic sensation caused by nicotine" (l.16-18). p. 44, l.21-24 The reference provided (Rabinoff et al.) does not represent a robust and credible scientific support. SCHEER's allegation referring to Rabinoff et al. should be deleted. The information concerning possible pharmacological effects of selected chemical tobacco additives presented by Rabinoff et al. suffers from poor scientific quality and is lacking seriousness. Tellingly, Rabinoff et al. link isovaleric acid to a "[p]ossible pheromone effect," explaining that "[i]sovaleric acid is a component of the pheromones present in the vaginal secretions responsible in the female rhesus monkey for stimulating sexual behavior in the male. It is also found to be one of the major components of the subauricular gland secretion of the male pronghorn (antelope); its odor produces a strong response from the male as indicated by sniffing, licking, marking, and thrashing." Such kind of narrative is far from a serious discussion of scientific questions. Rabinoff et al. is based on 117 references, 75 of which are not peer reviewed internal documents of the tobacco industry. Not one of the other 42 references in the publication of Rabinoff et al. is a study on additives performed by	Please see above. Actually, this is not inconsistent, as impact is used to describe both effects. Regarding the tobacco industry documents please refer to the following: The information gleaned from the documents assisted the WHO and its 192 member countries to negotiate the WHO Framework Convention on Tobacco Control (WHO FCTC), an international treaty intended to regulate the tobacco industry and its products in a uniform way. (For more information on the WHO FCTC, go to the web site of the WHO Tobacco Free Initiative: http://www.who.int/tobacco.) The information provided in these documents, as well as the reports that have been prepared describing their content, provide a wealth of information about some of the plans and processes of the tobacco companies in their attempt to delay or obstruct tobacco control measures and policies. Only a fraction of the documents' content has been explored, and additional knowledge about the tobacco companies' activities at the regional, national and local levels could assist policy-makers, government employees and nongovernmental organisations in the development of tobacco control strategies as the world moves towards the implementation of the WHO Framework Convention on Tobacco Control (WHO FCTC). http://www.who.int/tobacco/communications/TI_manual_content.pdfOn this basis, SCHEER only concludes based on the TPD.

			scientists of the tobacco industry published in peer reviewed scientific journals.	
120.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.3.6 Characterising flavour and inhalation facilitation as contribution to attractiveness	Art. 6.3 of the Directive states "…of the additive with other ingredients contained in the products concerned…". This requires any study to be performed in a mixture rather than through individual additives. Therefore, any assessment must be achieved through analysis of the tobacco products. The SCENIHR report of 2010 concluded that current methods are not adequate for a reliable quantification of attractiveness or addictiveness of nicotine and tobacco additives. There are no validated studies of any kind on attractiveness which would substantiate SCHEER's call for an attractiveness assessment. Furthermore, attractiveness does not fall within SCHEER's Mandate for this Preliminary Opinion 2. Page 41, Lines 8-13: No animal model currently exist for the assessment of attractiveness. We would also point out that no validated studies of any kind currently exist for this type of assessment. We also agree with the opinion that ethical considerations preclude human testing and are not clear whether SCHEER is endorsing this type of study. Page 41, Lines 35-39: All methods that inform regulatory measures must be robust, reproducible, and repeatable, and be based on robust scientific evidence. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology. Page 42, Lines 5-12:	Please see the answer to comment 1. Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". Human studies are indeed discouraged; they may be used (e.g. in case of flavour assessment), but only if the study subjects are not exposed to the harmful smoke emissions of tobacco products. Regarding implementation of characterising flavour assessment, the SCHEER refers to this webpage of the European Commission: http://ec.europa.eu/health/tobacco/products/implementation/characterising_flavours_en.htm. This information can be found via the webpage cited above; this

			SCHEER should provide information as to how the expert panel was constructed, including particularly details on appointment and training. SCHEER should also outline how any expert panel's findings would relate to typical consumer use.	reference is also included in the Opinion.
			SCHEER should provide guidelines as to the exposure levels to be use in any validated study, and what potency or concentration of the additive should be used to reflect consumer use.	This is outside the remit of our mandate. The SCHEER was not asked to give detailed protocols but to advise the Commission on a possible framework to help the MS in asking and Tobacco Industry (TI) to present sound data; in particular the ToR states: *The Committee is asked to advise the Commission on the* ***type and criteria for comprehensive studies*** *that should be requested*. It has been clarified upfront in the text.
			We remind SCHEER of the SCENIHR 2010 opinion that ethical considerations preclude human studies.	Please see above.
			Page 42, Line 26-31: Only data generated from test methods which have undergone method validation is requested.	Please see above.
			Page 43, Lines 8-10: SCHEER should provide the biological basis which supports the assertion "Additives that influence these sensory attributes… possibly facilitate smoking initiation." SCHEER also needs to provide evidence supporting its allegation that the addition of additives is in order to target different groups specifically.	References are provided in the sentences following the cited quote.
			Page 43, Lines 17-18: Sugars undergo extensive thermal degradation and therefore will not be present in the smoke. Indeed, sugars are only added to the product to replace the natural sugars in the tobacco which are lost during the curing process, a point which is noted in the Directive (Recital 17).	Sugars provide sweetness to the smoke by the caramel flavours that are generated upon combustion of sugars. The SCHEER adapted the text to explain this better.

			Page 43, Lines 18-21: SCHEER should recommend a validated in vitro assay to assess the sensory attributes described. Page 43, Lines 22-26: SCHEER should provide evidence for the assertions made about the chemosensory effects of pyrazines and further explain what is meant by "they may reinforce the learned behaviour of smoking, enhance elasticity and help optimise nicotine dosing." Page 44, Lines 25-28: Menthol and thymol are not etheric oils. Also as referred to in our response to the opinion on Menthol it is not an anaesthetic. We do not use thymol in our products. Page 45, Lines 13-14: The use of fMRI and PET machines for such a purpose would be an inappropriate use of medical resource.	Please see above. This is explained in the reference provided. Thank you for pointing this out, the sentence has been adapted for clarity. PET systems are often used outside the medical theatre, e.g. for research purposes.
121.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.6 Characterising flavour and inhalation facilitation as contribution to attractiveness	We suggest to delete all references to attractiveness, in particular, on p. 41: subtitle 2.4.3.6, l. 6-7, p. 41, l. 8-13, and on p. 44: l. 29-45, because attractiveness is not a relevant criterion under Art. 6 and Art. 7 TPD. The statement "[O]ver 80% of all cigarettes contain at least one flavour" may be correct for the Netherlands but is not correct from an EU-wide perspective. There are several markets in which the majority of cigarettes do not contain flavor additives. Hence, we suggest to change p. 41, l. 15-16 to "Over 80% of all Dutch cigarettes contain…" The hypothesis that some tobacco additives may	Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". The suggestion has been accepted and the text has been changed accordingly. This is why this section is called Characterising flavour and

			facilitate inhalation and therefore may increase nicotine uptake which may result in an increase in addictiveness is not related to "characterizing flavors". Therefore we suggest either deleting p. 42, l. 35 – p. 44, l. 28, because it does not contain guidance on methods which should be used in comprehensive studies according to Art. 6 TPD, or shifting this basic literature information to chapter 2.4.3.5 "addictiveness testing". We would also suggest to shift the section "Studying sensory effects" (p. 45, l. 11-27) to chapter 2.4.3.5 "addictiveness testing" because the information included in this part is clearly linked to "addictiveness" and not to "characterizing flavor". Furthermore, this section contains a couple of claims that are not supported by references. We would kindly request to either add references or delete the following unsupported claims: "In order to make the smoke less aversive and permit deeper inhalation, additives such as liquorice and menthol are used." (p. 44, l. 2-3) "As a result, coughing due to inhalation of irritating smoke is dampened and the smoker can inhale the smoke deeper (and more frequently)." (p. 44, l. 26-27) "The harshness depends partly on the tar/nicotine ratio, but may also be decreased by certain additives such as propylene glycol or levulinates. Tar provides a strong flavour and mouth sensation, masking the harsher, bitter taste of nicotine which may be unpalatable to new smokers and uncomfortable to established smokers" (p. 43, l. 45-48).	inhalation facilitation as contribution to attractiveness. The reference to the previous SCHENIHR Opinion has been added.

122.	Bosse, Andrea, DVAI - German Association of the Flavour Industry, info@dvai-dvrh.eu, Germany	2.4.3.6 Characterising flavour and inhalation facilitation as contribution to attractiveness	In Step 3 of the testing strategy of this SCHEER opinion characterising flavour is addressed. It is only possible to determine if a flavour which contains an additive such as Gerniol imparts a noticeable flavour other than tobacco by using appropriate sensory analysis. The impact of a certain flavouring substance on the whole product depends on the composition of the tobacco product. Therefore it is not possible to lay down certain amounts when a flavouring substance imparts a noticeable flavour other than tobacco.	This sentence has been adapted.
123.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.4.3.7 Interaction of the additive with other additives/ingredient	We acknowledge that tobacco smoke is a complex mixture, which is exactly why the only way to fully evaluate the effect of additives on the toxicity of tobacco products is by testing them in the presence of the tobacco itself [11], under conditions of use, and so relevant to consumer exposure, which in turn is the implicit aim of Article 6. This allows for interactions of the additives and their pyrolysis products with other smoke components to be accounted for. SCHEER's notes in relation to the inherent variability in composition for tobacco that "[i]n addition, tobacco being a natural product, its composition is variable over time from batch to batch even within the same brand" (p45:32). This is also why a number of the additives are used on tobacco – in order to balance out the inherent crop to crop variability of the tobacco itself; a fact that is overlooked in the earlier statements that assert that tobacco additives confer no benefit. SCHEER suggests that at present there is no restriction on the use of additives [p.45: 39]. Prior to the introduction of TPD2, there were legal restrictions on ingredients in many EU markets including France, Germany and Hungary, and a	The issue of mixture toxicity is a complex one. The SCHEER advices to follow the approach taken by the non-food SCs in its Opinion in which the additive model [as opposed to synergistic and antagonistic ones] and a component approach, are proposed as the best pragmatic way to asses toxicity of mixtures, unless specific data are available indicating that a different model has to be used. Although there will potentially be synergistic or antagonistic effects of the additive and its pyrolysis products within the smoke matrix, as well as pyrosynthesis reactions, the net effect of all these contributions is too complex to study and assess with the currently available methodologies. In addition, the SCHEER reiterated the rationale that the results of testing with a specific product cannot be generalised to all products and brands, having a different composition with respect to tobacco type, blend and additives. Actual testing of each single mixture is not feasible. Regarding the benefit, the SCHEER would like to clarify that the focus is on health benefit. The SCHEER refers to restriction in the number of additives used in a single product. This has been made clearer in the revised version.

			Voluntary Agreement in the UK. These governed either the nature of the additives which could be used in, for example, tobacco and non-tobacco materials, or the levels which could be used. The Opinion states that "'apparently beneficial' activities cannot justify their use as additives in tobacco products… by masking adverse symptoms caused by smoking (e.g., cough), preventing awareness in the consumer and reductions in cigarette consumption" [p. 45:46]. However, these assertions are made without evidence, as the Rabinoff paper cited by the Committee, provides no scientific evidence to support many of the allegations made. SCHEER made a special mention of the work of the EU project EuroMix [52], however, we note that this is a four year project not due to be completed until 2019, which is outside the timelines for the testing of the Priority Additives. We also note from EuroMix's own literature [52](that only a limited number of toxicological effects will be considered, such as "fatty changes in the liver, skeletal malformation and an example of an endocrine effect", which seem to be of limited value in assessing tobacco additives. Additionally, the project will include "[v]erification of in silico methods and the in vitro bioassay toolbox for mixture testing against in vivo animal tests" This seems at odds with SCHEER's comments regarding the acceptability of animal testing (Section 2.4.3.2, p25).	Please see answer to comment 119. In the paragraphs before the one making reference to the EuroMix projects all the relevant information and framework are provided for dealing with mixture toxicity from now on. The reference to Euromix is only given to advice that in the future other methodologies and framework would be likely available (the SCHEER was perfectly aware that it cannot be used at present and during the 18 months for presenting data on the 15 additives in the priority list). To make it clearer, the phrase 'in the future' has been added upfront to the paragraph citing the Project.
124.	Martinez, Javier, JT International SA, 8 rue	2.4.3.7 Interaction of the additive with	p. 45, l. 23-27 SCHEER refers to Rabinoff 2007 to assert that "in research projects conducted by Philip Morris from 1982 to 1995, electroencephalography (EEG), pattern reversal evoked potential (PREP),	Please see answer to comment 119.

	Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	other additives/ingredient	and chemo-sensory event-related potential (CSERP) were used to measure physiological, sensory, and cognitive changes related to nicotine and to cigarette additives." Rabinoff precisely cited a Philip Morris document (Bates no. 2056128216/8223) authored by Gullotta to support this claim. Nonetheless, following a review of this document, we note that Gullotta commented that "[n]evertheless, it is important to understand the PREP measures a CNS effect, but does not explicate it: the mechanism by which smoking or nicotine may cause a decrease in P1 [peak 1] latency was neither identified not studied in the research. …the decrease may be a consequence of, but not the reason for, smoking cigarettes." We have not identified any data associating a cognitive change with the presence of an additive in tobacco. This is pure speculation and should be removed. p. 45, l. 42-45 SCHEER refers to the Rabinoff et al. paper, which, based on their review of botanical medicine sources, indicates "that many botanical and phyto-chemical additives have other properties, including anesthetic, antibacterial, anticancer, anti-inflammatory, antifungal, and antiviral properties." The reference provided (Rabinoff et al.) does not represent a robust and credible scientific support. SCHEER's allegation referring to Rabinoff et al. should be deleted. p. 47 l. 4-12 Please add that virtually all nicotine inhaled in mainstream smoke is rapidly absorbed in the upper respiratory tract and lungs, regardless of the "smoke pH" of cigarette mainstream smoke (MS), discounting the importance of MS gas phase/particulate phase fraction or ratio of protonated/nonprotonated nicotine.	Please see answer to comment 119. It is correct that the percentage absorption of nicotine from smoking is almost 100%. However, absorption is not the most interesting aspect mentioned in this paragraph, but it is rather nicotine bioavailability. Bioavailability is defined by an optimal rate of adsorption and distribution from the lungs into the bloodstream.

			p. 49, l. 4, p. 52, l. 22, p. 53 l.29: The SCHEER's claim that "[s]everal pyrazines are also added as additives to cigarettes to impart flavour to low tar cigarettes" is speculative. Please this should be deleted. The SCHEER refers to Alpert 2015 to support this claim. While, we could not locate the complete reference related to this cite absent in SCHEER references list, we identified a study authored by Alpert 2016 (Alpert HR, et al. Tob Control 2016;25: 444–450) The authors refer to internal tobacco industry documents, which are not peer reviewed. Notably, Alpert et al. pointed out that "Research conducted by industry is for business and commercial purposes, has not been peer reviewed and cannot be considered to be conclusive, absent independent confirmation. Therefore, a larger body of evidence should be considered with respect to the implications of these findings for public health and policy." Alpert et al. reported, e.g., : "…Such additives may enhance dependence", "Pyrazine stimulation of olfactory receptors may enhance learned behavior", "Pyrazines may act in concert with nicotine", The sensory inputs of pyrazine flavour additives might also provide cues for reward-related learned behaviours and could play a critical role in the development, maintenance and relapse of tobacco dependence." Nevertheless, "could" and "may" do not represent robust research support and are an indirect way of conceding that no real scientific foundation exists to support this claim. The reference by Alpert does not represent a robust and credible scientific support and should be deleted.	Please see answer to comment 119.
125.	Simms, Liam, Imperial Tobacco Limited,	2.4.3.7 Interaction of the additive with	Page 45, Lines 42-45: No communications to this effect are made to our consumers. Additives may be added to tobacco products during manufacture. Additives (for	The SCHEER does not imply in the text that such claims are made.

	liam.simms@uk.imptob.com, United Kingdom	other additives/ingredient	example, flavourings typically used in food) are used in very small quantities in some brands. They are used to enhance their overall flavour characteristics and aroma, giving brand variants their own distinctive style, in line with consumer preferences. Imperial Tobacco Ltd does not add anything to our products to make it more difficult for smokers to stop smoking, to make our products attractive to children or to increase the level or change the chemical form of nicotine in tobacco smoke. Additionally, due to the known health risks of smoking, we do not claim that tobacco products are "safe", neither do we make claims that any Tobacco Product is "safer" than another (unless endorsed and/or required by regulatory authorities). Pages 46, Lines 3-9: Additives may be added to tobacco products during manufacture. Additives (for example, flavourings typically used in food) are used in very small quantities in some brands to enhance their overall flavour characteristics and aroma, giving brand variants their own distinctive style, in line with consumer preferences. We assess the appropriateness and acceptability of the additives we use. We employ a panel of experienced toxicologists to carry out risk assessments on additives and conduct risk assessments on the suitability of these additives for inclusion in our products. Page 46, Lines 10-18: The behaviour of additives in a cigarette with a complex mixture of additives has already been	This is not inconsistent with the lines the comments refer to. Please see the answer to comment 1.

			investigated by Baker, et al., (2004), Carmines et al., (2002), Gaworski et al., (1999), Gaworski et al., (1998), and Renne et al., (2006). The mixtures of additives did not significantly change the biological activity of the smoke in these studies. Pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. Page 47, Lines 4-12: It would benefit the reader to provide an appropriate reference or to delete this point if it cannot be substantiated. In this Preliminary Opinion 2, SCHEER outline several hypotheses, not validated by scientific evidence, and contradicting available research (Mueller et al. 2000). We support evidence based on robust methods and credible scientific research, on which valid assessment can be based. Page 47, Lines 11 to 12: We agree with SCHEER, that these actions are "non-relevant". Page 47, Lines 21-37: As in the response to Page 45, Lines 42-45, no communications to this effect are made to our consumers. Additives may be added to tobacco products during manufacture. additives (for example, flavourings typically used in food) are used in very small quantities in some brands to enhance their overall flavour characteristics and aroma, giving brand variants their own distinctive style, in line with consumer preferences. Additionally, due to the known health risks of smoking, we do not claim that tobacco products are	Please see the previous answers, such as comment 72. The reference to the SCENIHR Opinion 2010 has been added. Thank you for your agreement. The SCHEER does not imply in the text that such claims are made.

			"safe", neither do we make claims that any Tobacco Product is "safer" than another (unless endorsed and/or required by regulatory authorities).	
126.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.4.3.7 Interaction of the additive with other additives/ingredient	We suggest delete the sentence (p. 45, l. 42-45): "These botanical (…) tobacco products" as tobacco additives are not used for any of these supposed properties but for the physical integrity and engineering/manufacturing of the products, for consumer acceptability as well as to partially replenish the sugar that is lost during the air curing process of Burley tobacco (Roemer et al., 2010). Please provide supporting references for the following claims or delete them if unsupported: P. 45, l. 46 - p. 46, l. 2: "Indeed, in some cases, they provide for a "smoother" smoking experience by masking adverse symptoms caused by smoking (e.g., cough), preventing awareness in the consumer and reductions in cigarette consumption." P. 46, l. 5-9: "This 'optimal' mixture of additives is intentionally added to a known toxic, carcinogenic and addictive product in order to make the product more palatable by masking the bitter taste, improving the flavour and reduce the irritation of inhaled smoke, optimising nicotine uptake." We suggest to delete sections p. 46, l. 25 – l. 46 and p. 47, l. 13 - 37 because they do not contain information about the methodology the industry needs to apply to test the priority additives. The TPD has already set a framework for the testing and it was decided not to use other frameworks such as EFSA or ECHA. Please consider deleting the sentence at p. 47 l. 31-	These products have been acknowledged as efficient nicotine delivery products. For further explanation see answer to comment 119. The reference to the SCENIHR Opinion 2010 has been added. See answer above and also to comment 119. See answer above and also to comment 119. Please see the Article 7 of Directive 2014/40/EU foresees in

			32): "Usage of fruit (…) under the TPD Article 7 2 a" as Art. 7(2) and Art. 7(6) TPD are neither in SCHEER's mandate nor relevant for enhanced reporting obligations.	particular **the prohibition of the following**: 1) tobacco products with a characterising flavour. (Art 7(1)) 2) tobacco products containing the following additives2 (Art 7(6)): a) vitamins or other additives that create the impression that a tobacco product has a health benefit or presents reduced health risks; b) caffeine or taurine or other additives and stimulant compounds that are associated with energy and vitality; c) additives with colouring properties for emissions; d) for tobacco products for smoking, additives that facilitate inhalation or nicotine uptake; and **e) additives that have CMR3 properties in unburnt form.** On this basis, the SCHEER only concludes based on the TPD.
127.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.4.4 Step 4: Reporting	We agree with SCHEER's recommendation to submit a single format report for all countries including an evaluation of all available information. We also agree that the burden on industry and authorities could be reduced by the formation of consortia and the submission of joint reports. SCHEER should provide guidance on the submission of these reports and contingency arrangements in the case that multiple reports are submitted containing different information. SCHEER should provide guidance on the criteria that these reports will be evaluated against and provide details of the consequences if the information provided is not acceptable to the independent institutes	Thank you for the positive comments. This is outside the SCHEER mandate. This is outside the SCHEER mandate.
128.	Ureel, Ludwig, British American	2.4.4 Step 4: Reporting	Not all original (raw) data is available for submission for historical studies. For example, for the Baker papers [1] [2] [3] the inhalation study	This is outside the SCHEER mandate. The same issues are valid also for the other regulatory frameworks. The request for reporting asked to TI is far to be more onerous than for other

	Tobacco, ludwig_ureel @bat.com, United Kingdom		was carried out at a contract laboratory in 2001/2002, and final reports were issued. However, at that time submission of the raw data was not required, and it is highly unlikely that the raw data is still available. Furthermore, external requirements are for the CRO to keep for a minimum of three GLP cycles, so a minimum of 6 years. For many of the items listed as requirements for the summary document, such information will not be included in the published scientific literature, and even to mark the entries as N/A will be an onerous task.	sectors.
129.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5 Specific knowledge gaps for the priority list tobacco additives	We note that for many of the statements made in the Opinion, SCHEER has failed to give any references, or evidence in support of their allegations.	Please refer to Opinion 1.
130.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5 Specific knowledge gaps for the priority list tobacco additives	For the reasons set forth in our comment to section 2, please consider changing the title to "Specific knowledge gaps for the priority list of additives used in cigarettes and roll-your-own tobacco". SCHEER is relying on SCENIHR's analysis of "major data gaps already identified in Tobacco Opinion 1 for the 15 additives" (see, e.g., Abstract at p. 5, l. 5). We disagree with some of SCENIHR's analysis and refer in this respect to our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", in which we stated (comment to the Abstract): "Had the Committee carried out a comprehensive	The comment was accepted and the title has been modified. Note that the specification has been added in many other parts of the text in the revised version. Please see the answer given to the same comment received for Opinion 1. In Opinion 1 the SCENIHR was not asked to carry out a risk assessment but a prioritisation based on hazard of a large number of additives. Opinion 1 served, as stipulated in the methodology, to the compilation of a priority list. This list will assist, in line with Article 6 of Directive 2014/40/EU, the Commission to develop priority list of at least 15 additives for which enhanced reporting obligations will apply (as described in the section 1 'background').

			review of all the evidence, it would have realized that most of the "gaps" it identified are in fact not gaps in the current state of science but in its literature research. Prior to requesting additional testing from manufacturers, it is essential to have completely assessed existing data and evidence. In particular, SCENIHR would have realized that, contrary to its statements, inhalation toxicity data (p.4, l.43), data on pyrolysis and exposure to combustion reactions products (p.4, l.45) and data on mixture toxicity (P.5, l.2) are not "scarce" or "negligible" but have been reported in peer reviewed publications not yet considered by SCENIHR, which we upload in the corresponding sections." We have not changed our views in this respect. In our view, and as correctly stated in the title, SCHEER is addressing "specific", not "major" data gaps. We suggest to amend the term "major" on p. 48, l. 2 to "specific".	The SCHEER view does not change. However, in order to clarify, some wording has been modified. The comment was accepted and the text was modified accordingly.
131.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.1 Carob bean	In a number of studies, an assortment of carob bean additives have been pyrolysed under conditions which simulated those of a burning cigarette [5] These studies demonstrate that whilst carob largely breaks down, many of the constituents reported by the Committee are not formed (although small amounts of furfural were produced). Whilst carob bean extract does contain polysaccharides, the evidence does not support the statement in the Opinion that on combustion acetaldehyde, acrolein and 2-furfural are generated and transfer into the mainstream smoke [p. 48:28]. For example, during cigarette combustion, groups of tobacco additives, including carob bean extract, at	In more recent study of Coggins et el, 2011 (Christopher R.E. Coggins, Jeffery S. Edmiston, Ann M. Jerome, Timothy B. Langston, Erica J. Sena, Donna C. Smith, and Michael J. Oldham. A comprehensive evaluation of the toxicology of cigarette ingredients: essential oils and resins. *Inhalation Toxicology*, 2011; 23(S1): 41–69) formation of additional (to control cigarette mainstream smoke levels) formaldehyde, benzene, B[a]P, acrylonitrile and other compounds has been reported. Furfural was found as a carob bean extract pyrolysis product in another study (Baker & Bishop (2004)).

			an application level of 0.7% generally reduced the levels of most of the measured smoke constituents, although a slight increase was recorded in the level of formaldehyde [1] [2] [3] However, these changes did not result in any impact on the in vitro or in vivo biological activity of the mainstream tobacco smoke. The findings of these studies are consistent with other extensive data sets also available in the public domain. As stated in the Opinion, carob bean extract is a complex natural material [p. 48:38] so it is logical to test it as such, to take account of interactions between compounds and possible additive effects. However, it is important to note that there is no evidence in support of the Opinion's claim that carob bean extract contains psychoactive chemicals [p. 48:41]. The assertion that aldehydes formed during combustion potentiate nicotine addiction is not scientifically proven and does not take into account available scientific knowledge. As previously reported by SCENIHR, [44](very few studies have been able to identify acetaldehyde in the blood of smokers, and those that have only managed to find it in very small and biologically insignificant concentrations, i.e. below those required to exert an effect in the brain. Whilst animal studies have indicated that aldehydes increase nicotine self-administration, such studies have involved the injection of large amounts of aldehydes, many orders of magnitude higher than those reached in the blood of smokers. It should also be noted that the 2010 SCENIHR report [44] (dismissed the potential for aldehydes in potentiating addiction, suggesting "no (indirect)	 The text in the Opinion was modified. The text concerning acetaldehyde in the Opinion was modified.

			addictive effect of sugars when used as a tobacco additive" and that due to its exhalation "it is uncertain whether the acetaldehyde in smoke contributes significantly to the blood level of this substance." The assessment outlined in step 2 is recommended to include the interaction/synergistic effect with other additives and tobacco chemicals. However, it is difficult to see how this could be achieved without the utilisation of comparative pyrolysis studies using a tobacco matrix – an approach that the Opinion explicitly rejects. In rejecting comparative testing, the Opinion fails to suggest any alternative approach to measure the interaction/synergistic effect with tobacco chemicals. The assessment also suggests assessment of palatability which, apart from being out of the scope of Article 6, cannot be effectively measured without humans smoking the products – an approach that has also been explicitly ruled out earlier in this Opinion [section 2.4.3.2 lines 35-36].	Please see the replies to the previous comments on pyrolysis (n° 72) and comparative testing (n°1). The SCHEER disagrees. See statement e.g. in the Abstract*: " Human studies are generally discouraged; they may be used (e.g. in case of flavour assessment), but only if the study subjects are informed and not exposed to the harmful smoke emissions of tobacco products".*
132.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.1 Carob bean	p.48, l.32-34 Please delete that "[c]onverging data indicate that MAO (monoamine oxidase) inhibitors contained in tobacco and tobacco smoke act synergistically with nicotine to enhance addiction potential." No evidence is available to support this claim. Berlin and Anthenelli 2001 conceded that their conclusion regarding MAO inhibition by compounds found in tobacco smoke or tobacco can potentiate nicotine's effect is "speculation". To our knowledge, no additional information has altered this conclusion. Please refer to a more recent review (Hogg et al. 2016) that described the available data related to a role of MAO inhibition in tobacco dependence. The authors pointed out that "no data	Text on MAO and acetaldehyde has been modified in the final Opinion to be more specific.

			were identified to support the hypothesis that MAO inhibitors in or derived from tobacco or tobacco additives affect tobacco dependence in human smokers." Please mention that the SCENIHR 2010 report commented that substances that supposedly inhibit MAO are naturally present in tobacco leaves, not added as additives. The SCENIHR 2010 stated: "The addictiveness of nicotine is enforced by substances in tobacco leaves that inhibit the action of monoamine oxidase (MAO) in the body."	
			p.48, l.35-36 The concepts of "harshness and smoothness" and "impact and smoothness "are irrelevant and should be removed. Only taste and smell are considered in the definition for characterizing flavor provided by the TPD2.	Harshness and smoothness are discussed in the context of facilitating inhalation or nicotine uptake, which are described in the TPD2.
			p.49, l.14-15 Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement.	See the replies to the comment (e.g. 47 or 72) on pyrolysis.
			Please note that studies related to pyrolysis of carob bean are available. (Baker and Bishop, 2005). Several studies have been used to assess mixtures of additives applied to experimental cigarettes (Carmines et al., 2002; Baker et al., 2004 a-c; Renne et al., 2006), while others have focused on single additives (Heck et al., 2002; Lemus et al., 2007; Stavanja et al., 2008; Coggins et al. 2011 a-i; Gaworski et al., 2011). Please note that tobacco	All cited studies were comparative testing studies, therefore please see the answer on limitation of comparative testing (comment 1).

			smoke from test cigarettes containing carob bean at levels up to 42,300 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding carob bean. p.49, l.5-7+ l.20 Please remove the sentence related to palatability. "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. The reference regarding "attractiveness" is irrelevant and should be removed. p.49, l.16-19 The guidance provided by SCHEER goes beyond requirements as defined in of the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, "addictiveness" and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Therefore, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, "addictiveness" or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation.	Please see the answer to comment 1.
133.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.co	2.5.1 Carob bean	Page 48 Lines 28-37: SCHEER should reference the page in SCENIHR 2010 where this is stated. Page 49, Lines 12-14: Pyrolysis studies are not representative under the	Typically the reference is cited and not the particular page.

	m, United Kingdom		conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. SCHEER should be aware that there are various studies in the public literature which assess the behaviour of carob bean extract in a combusted cigarette and its biological effects (Baker et al., (2004), Carmines et al., (2002), Gaworski et al., (1998) and Gaworski et al., (1999) in some cases magnitudes higher than those used for commercial cigarettes. Even under these exaggerated inclusions, no significant differences between control and test cigarettes were observed in any of these studies. Page 49, Lines 19-22: We recommend that only data generated from test methods which have undergone method validation is requested. The OECD (2005) defines method validation as "…a process based on scientifically sound principles by which the reliability and relevance of a particular test, approach, method or process are established for a specific purpose". Test methods which have not been validated, nor gained international regulatory acceptance could give misleading results as the reliability and relevance of the method has not been established (Hartung et al., 2004). Consequently, it is unscientific to use assays lacking proper validation.	Please see our answer on pyrolysis (n°72) and comparative testing (n°1). This recommendation is very valid, and most of the tests which may be applied have been validated. However, it is the ideal situation and in very exceptional cases non-validated methods of good quality may be accepted.
134.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com,	2.5.1 Carob bean	SCHEER is relying on SCENIHR's "rational for inclusion" for carob been set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.8 Carob bean extract). We have	The text was modified. Please see the answer on pyrolysis (n°72) and comparative testing (n°1).

	Other		not changed our views in this respect and therefore recommend the following changes: We suggest replacing the word "likely" with "suspected that" on p. 48, l. 30 because currently there is no scientific basis to assume likelihood. Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD, we suggest to amend the sentence on p. 48 l. 34 – 37 as follows "Carob bean extract has a sweet, fruity, chocolaty flavour and thereby reduces the harshness of smoking." As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 7 (9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to replace "In case of (…) should be presented (Step4)" (p. 49, l. 16 – 19) with "In case of positive results for genotoxicity/carcinogenicity of its pyrolysis products additional testing would be required to continue with Step 3 in order to generate additional data for a Weight of Evidence assessment."	The comment has been accepted and the text has been changed accordingly. Please see our previous answer to the same topic.
135.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.5.1 Carob bean	*Repetition of comment 11*	Please refer to answer to comment n°11.
136.	Thielen, Anja, Deutscher Zigarettenver	2.5.1 Carob bean	*Repetition of comment 11*	Please refer to answer to comment n°11.

	band, a.thielen@zigarettenverband.de, Germany			
137.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.10 Liquorice	p.58,l.32-34 Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. p.58,l. 3-6 A review by van Andel et al. 2003 conducted by RIVM could not find any evidence for any bronchodilation effects of glycyrrhizic acid (Glycyrrhizin) from their extensive literature search. Consequently, please remove l. 3-6. p.58,l. 38-40, p.59, l. 3-6: Please remove these lines. No scientific data support the claim that bronchodilation affect smoking inhalation patterns or smoking behavior. Please refer here to a RIVM review on the glycyrrhizic acid component of liquorice used in tobacco products. The authors concluded that "[n]o data are available on the dependence potential of glycyrrhizic acid". According to the RIVM, "[t]he statement that glycyrrhizic acid acts as a bronchodilatator could not be confirmed from the currently available literature." Please consider the Müller and Röper article, which reported that glycyrrhizin was thermolabile and would not transfer intact to cigarette mainstream smoke in sufficient amounts.	On p.58, l. 32-34, it has been replaced by "facilitating inhalation and resulting in characterising flavour". On p.59, l. 3-6: the SCHEER disagrees. Since this represents a grey area, scientific tests will be able to reveal whether or not glycyrrhizin induces a bronchodilator effect. However, the text has been clarified (please note that this part was a copy and paste text taken from the previous Opinion).

			We are not aware of any additional information that has altered this conclusion. Please refer to a recent study by van Dijk et al. who invalidated the hypothesis that bronchodilation increases the pulmonary retention of cigarette smoke. p.59,l.1-3, l.11-13 Licorice was investigated in pyrolysis studies by Baker & Bishop 2005, Carmines et al., 2005 and Purkis et al., 2011. Pyrolysis products of licorice were not increased in the smoke of experimental cigarette to which liquorice had been added (Carmines et al., 2005). This approach is consistent with TPD2 requirement, Article 6(2) (a), (d) and Article 7(9), to test under the condition of use. Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement. p.59,l.8-10 Please mention that glycyrrhizinic acid and its derivatives have previously been reported to give both positive and negative mutagenicity results. In the Scientific Committee on Food (SCF) 2003 opinion for glycyrrhizinic acid and its ammonium salt, the committee concluded that, based on all available data, glycyrrhizinic acid and glycyrrhetic acid are considered to be non-genotoxic. More recently, the results generated by Chandrasekaran et al. 2011 provide support to the non-genotoxic activity of licorice/licorice extract. A long term feeding study using disodium	On p.59, l.1-3, l.11-13: For this reason, the SCHEER proposed in the Opinion (paragraph 3.4.2.2) "When it is suspected that such reactions will occur, one may consider pyrolysing a simple mixture containing the additive together with the component with which reaction is foreseen (either with the component itself or with its pyrolysis products". Furthermore, please refer to our general statement on comparative testing (see answer n°1 to comment n°1). On p.59, l.8-10: it has been mentioned: Glycyrrhizinic acid and its derivatives have previously been reported to give both positive and negative mutagenicity results.

			glycyrrhizinate (a constituent in licorice) failed to show tumorigenic activity. (Kobuke et al.1985) p.59, l.38-40 Please note that Tobacco smoke from test cigarettes containing licorice at levels up to 12.5% and additive free reference cigarettes was tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding licorice. Carmines et al. 2005. Carmines, 2002 & Rustemeier et al. 2002, Baker et al. 2004a Roemer et (al. 2002, Baker et al., 2004c, Gaworski et al. 1998, Vanscheeuwijck et al. 2002, Gaworski et al. 1999.)	On p.59, l.38-40: the high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough would be available they could be used. The SCHEER indeed stated in the Preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. Please see the answer n°1 to comment n°1.
138.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.10 Liquorice	As described in the Opinion [p.58:30], liquorice is a complex natural material which contains numerous substances; a major constituent of which is glycyrrhizin, also known as glycyrrhizic acid. We agree with SCHEER that glycyrrhizin is biologically active when administered orally, and that high doses of liquorice in the diet are associated with adverse effects. However, as described in a previous RIVM review [36], "…it is improbable that the intake of glycyrrhizic acid during cigarette smoking will exceed the daily oral intake". In fact RIVM continued, "Glycyrrhyzic acid is metabolised in the gastrointestinal tract into glycyrrhetic acid, its biologically active metabolite. It is unlikely that this metabolisation can occur after inhalation. Therefore it is also unlikely that smoking-related exposure to glycyrrhizic acid, in analogy with excessive liquorice candy intake, will increase mineralocorticoid activity and result under some conditions in hypertension".	On p.59, l.32-37 it has been mentioned: Since the oral absorption has been demonstrated to be high, the systemic toxicity after inhalation (also assuming a total absorption through the lung (100%) the effects are not expected to be different. Since the relevant NOAEL is relatively high (2 mg glycyrrhizic acid / kg bw per day for healthy volunteers) and the blood serum half-life is 5 hours, the risk of systemic general toxicity may not be high at the doses used as tobacco additive.

			We are not aware of any additional information published since then which is likely to have altered this conclusion. Studies have demonstrated that liquorice breaks down on pyrolysis under conditions which simulated those of a burning cigarette [5], but that compounds of concern are only minor constituents of the pyrolysate. It was recognised that less severe decomposition of non-volatile additives occurs in a burning cigarette relative to the pyrolysis system. This was illustrated by the data obtained when liquorice was included in a test cigarette at 2%, and compared to an additive free control product, which demonstrated that the mainstream smoke yields of these constituents were not increased [5], and in fact the levels of most of the measured smoke constituents were reduced. As an additive used by BAT, liquorice has been evaluated in a number of biological assays, such as in vitro genotoxicity tests, and 90-day in vivo inhalation studies. The results of these studies indicate that, in the assays performed, there is no greater toxicological effect from cigarettes containing liquorice at a 2% inclusion level, when compared to those without. These results, which have been published in peer reviewed journals [1] [2] [3], are consistent with other extensive data sets also available in the public domain. Studies have been conducted on the inclusion of liquorice at much higher levels than in the tobacco industry [13]. The results demonstrate an increased biological effect at 12.5% inclusion. Whilst this is a far greater inclusion than is realistic, it does demonstrate that comparative studies are able to	The high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough would be available they could be used. The SCHEER indeed stated in the preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. Please see the answer n°1 to comment n°1. Please see the comment above. The potential genotoxic effects of liquorice extract have been postulated. Glycyrrhizinic acid and its derivatives have previously been reported to give both positive and negative mutagenicity results.

			detect changes provided they are significant.	
139.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.10 Liquorice	Page 58, Lines 30-31: This statement appears to be derived from a material safety datasheet and is not applicable at the levels liquorice is added to a cigarette. Page 58, Lines 38-40: No evidence is provided to support this statement. In this Preliminary Opinion SCHEER outline several hypotheses, not validated by scientific evidence, and contradicting available research (Mueller et al., 2000). We support evidence based on robust methods and credible scientific research, on which valid assessment can be based. Page 59, Lines 11-13; No validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. Page 59, Lines 14-37: It should be noted by SCHEER that pyrolysis studies show that liquorice extract is extensively pyrolysed with no components expected to transfer intact into mainstream smoke (Carmines et al., 2005). Purkis et al., (2011) observed in cigarette smoke chemistry study that "the non-volatile ammonium salt of glycyrrhizic acid was not recovered intact either in mainstream or side stream smoke and it was therefore concluded that it underwent full degradation". Therefore, the components of liquorice extract SCHEER mentions are not of concern as they are extensively broken down in a burning cigarette.	On p.58, l.30-31: the text has been clarified On p.58, l.38-40: the text has been clarified On p.59, l.11-13, l. 14-37: the high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough would be available they could be used. The SCHEER indeed stated in the preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. Please see the answer n°1 to comment n°1 and other answer related to the general issue of pyrolysis.

			Page 59, Lines 38-42: SCHEER should be aware that there are various studies in the public literature which assess the behaviour of liquorice extract in a combusted cigarette and its biological effects (Baker et al., (2004), Carmines et al., (2002), Carmines et al., (2005), Gaworski et al., (1998) and Gaworski et al., (1999) at levels several magnitudes higher than what are traditionally used for commercial cigarettes. No significant differences between control and test cigarettes were observed in any of these studies.	On p.59, l.38-42: please see the comment above.
140.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.10 Liquorice	SCHEER is relying on SCENIHR's "rational for inclusion" for liquorice set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.18 Liquorice). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete "thereby enhancing the attractiveness of smoking" on p. 58, l. 34. As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 6(2), (3) and Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to delete on p. 59 l. 14 "In case results are negative."	 On p.58, l.34: now in the text: Liquorice extracts are used to improve the organoleptic properties of tobacco smoke, making the harsh cigarette smoke palatable, thereby facilitating inhalation and resulting in characterising flavour See the previous answer.

141.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.11 Maltol	Please note that in September 2015, the European Food Standards Agency (EFSA) ruled out the genotoxicity of Maltol, EFSA, CEF Panel (2015).	EFSA only studies oral uptake of compounds and not the inhalation route. The toxic effect of inhaled compounds can differ from ingested compound because the route dependent metabolism can take place. However, if genotoxicity of Maltol is definitely ruled out, as a result of step 1, the additive could enter the procedure and be evaluated. Please check the reference for the real conclusion on maltol genotoxicity. Moreover as mentioned in the Opinion it is also the fact that maltol is a potential anti-apoptotic compound that makes this compound potentially hazardous.
142.	Ureel, Ludwig, British American Tobacco, ludwig_ureel@bat.com, United Kingdom	2.5.11 Maltol	We would like to draw the attention of SCHEER to the present revision of FGE.213 (FGE.213Rev2), adopted by EFSA on 9 September 2015 [39]. This includes new data provided by the flavour industry which resulted in the EFSA Panel agreeing that "the negative result of the in vivo micronucleus assay can be considered reliable and, accordingly, the concern for genotoxicity for maltol [FL-no: 07.014] … is ruled out" [39]. In another study, Maltol was tested in a pyrolysis system which simulated the conditions of a burning cigarette [4]. Results demonstrated that over 99.8% of the parent compound transferred unchanged. Pyrolytic breakdown products were estimated to equate to less than 0.2µg/cigarette based on typical application level of the parent compound.	The reference [39] is not correctly cited. The following lines have been copied from the summary: 'In the case of maltol, positive results were observed in an in vitro micronucleus assay in human peripheral blood lymphocytes and in an in vivo micronucleus assay in mouse bone marrow after intraperitoneal application. Maltol was also tested in rats (administered by gavage) in a combined bone marrow micronucleus assay and comet assay in liver. Both tests showed negative results, but no clinical signs and no bone marrow toxicity were observed. To investigate the systemic exposure, plasma bioanalysis was performed, but results were inconsistent. Owing to the intended use of maltol as a food-flavouring agent, the in vivo study performed with administration of maltol by gavage is considered more relevant than the study performed by intraperitoneal application. Therefore, the Panel concluded in Revision 1 of this FGE that for maltol [FL-no: 07.014] and maltyl isobutyrate [FLno: 09.525] **the concern for genotoxicity could not be ruled out.**' This is correct and that is one of reasons why maltol is taken up in the list of the Opinion, the compound is not destroyed by pyrolysis but is inhaled.

			We are surprised to see the comments regarding the possible effects of maltol on the central nervous system (p.60:10). Given that the additive itself has no harmonised classification under Regulation (EC) No 1272/2008, no such effects were identified by over 900 notifiers [40], and the in vitro study which appears to be the foundation of such claims used exposures far higher than experienced during smoking.	Ref [40] is a screenshot of a summary for labelling and classification (of the ECHA website). The interpretation that such effects were not identified for labelling does not mean that the compound is thorough been tested for such effects (in many case the reference could be data lacking).
143.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.11 Maltol	Page 60, Lines 7-17: After the consideration of new data, EFSA have concluded that the concern for genotoxicity for Maltol in food can be ruled out (EFSA, 2015: Scientific opinion on flavouring group evaluation 213, revision2: FGE.213Rev2). Maltol was negative in a combined in vivo comet and micronucleus assay (Beevers, 2013, as cited in EFSA 2014). Data for the in vivo comet and micronucleus assay was considered along with data to prove systemic availability of maltol after dosing (Beevers, 2013 as cited in EFSA 2014), which had been requested in a previous evaluation by EFSA. In FGE. 213Rev1 (EFSA, 2014) this data was considered but there were questions around the plasma analysis of the maltol levels. New data for plasma analysis of maltol was subsequently submitted by the flavour industry (Beevers, 2015 as cited in EFSA 2015). EFSA have now concluded, in FGE.213 Rev2 (EFSA, 2015), that based on the data now available for maltol, the concern for genotoxicity can be ruled out.	See the reply to the comment 142.
144.	Martinez,	2.5.12	p.60, l.38-39; p.61, l.33-36 + p.62, l.5; P. 61, l.39,	The evidence available is considered convincing enough.

	Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	Menthol	No robust scientific data support the claims that "menthol …facilitates deeper inhalation and adds to the impact of nicotine." Please retract this statement. SCENIHR itself underscored the speculative nature of these allegations, stating in 2010:"It has been proposed, that the cooling and local anesthetic effects [of menthol] could lead to deeper inhalation of the smoke and higher exposure to other smoke constituents, but current data are inconclusive". Accordingly, FDA PSE 2013 stated: "the weight of evidence supports the conclusion that menthol in cigarettes is likely not associated with increased or decreased levels of biomarkers of exposure." Numerous studies disagree with the SCHEER claiming that "smokers usually using menthol cigarettes develop greater nicotine dependence" and "menthol cigarette smokers are less successful quitting smoking." Please refer to the study by Hyland et al., which, represents one of the most widely cited in the published literature with respect to the possible effects of menthol on smoking behavior. The authors reported that mentholated cigarette smokers do not exhibit greater signs of nicotine dependence. (see also Murray et al.). Cubbin et al. reported that menthol smokers do not have a harder time quitting compared with non-menthol smokers. These results have been recently echoed by a recent study (Keeler et al.) indicating no significant difference in either successful cessation or intention-to-quit between menthol and non-menthol smokers. Please refer to the 2016 WHO Advisory providing: "Both TPSAC 2011 and the FDA (2013a) raised concern about the quality of the data available on cessation outcomes. No studies were found that were designed specifically to evaluate the role of menthol cigarettes in cessation. … The results on quit rates among white menthol and non-menthol	Secondary sources of information used as evaluations carried out by other Agencies (i.e. EFSA or US-EPA) were considered fully reliable. The same for the additives evaluated by the PITOC project: the information included in the fact-sheet was complied from an extensive literature search and evaluation up to 2012. More recent data was added by SCHEER. The literature cited was not considered convincing enough to lead to changes in the Opinion. For instance, Hyland concludes that "some biologic evidence suggests that menthol may facilitate greater nicotine transfer to the pulmonary system" and that further work is needed. Hyland does not conclude that "mentholated cigarette smokers do not exhibit greater signs of nicotine dependence" (comment from JT International), but that "No consistent associations were observed for menthol use and indicators of dependence".

			cigarette smokers were inconclusive." Taken together, the evidence from these references alone should be more than sufficient to preclude SCHEER from concluding that "menthol cigarette smokers develop greater nicotine dependence" or "are less successful in quitting."	
			Please note that the scientific literature does not support claims related to an increase in disease risk associated with menthol cigarette smoking relative to nonmenthol brands. (Heck et al.) The results of a study conducted by the FDA indicated that "[a]ll-cause mortality net of lung cancer mortality did not differ for menthol and nonmenthol smokers."(Rostron et al. 2012) Accordingly, the WHO IARC 2012 noted that "Studies have generally not demonstrated an increased risk of lung cancer for mentholated cigarettes versus non-mentholated cigarettes." SCHEER fails to mention that the FDA (2013) concluded that "the weight of evidence supports the conclusion that menthol in cigarettes is not associated with an increase in disease risk to the user." Notably, the recent WHO 2016 Advisory note states: "There is no strong evidence that use of menthol cigarettes increases the delivery or toxicity of smoke or biomarkers of exposure to nicotine or toxicants." Please refer to Munro et al. who recently reported that "Smoking regardless of cigarette type is hazardous to health, but these results do not indicate that menthol cigarettes are associated with greater CVD risks than non-menthol cigarettes." p.62, l.13-16	The SCHEER agrees that menthol cigarettes per se are not more toxic than menthol-free cigarettes. However, indirect toxicity was established (see also Opinion I): adequate data indicate that menthol presence is associated with increased smoking initiation and greater addiction, especially among young people, as confirmed later by the studies of Nonnemaker et al. (2013) and Brennan et al. (2015). WHO indeed concludes that there no STRONG evidence, but also that "Several reviews have commented on the shortcomings of the available epidemiological, clinical and laboratory research on menthol cigarettes . . . and it is difficult to draw meaningful conclusions.
			Please add that the nature of menthol pyrolysis products was investigated in a pyrolysis study (Baker & Bishop 2004). Please mention that pyrolysis studies show the intact transfer of 97.4 % of menthol. (Jenkins 1970). Please add that Purkis et al. 2011 reported that pyrolysis does not provide	The pyrolysis results of Baker & Bishop and others were accidentally not included in Opinion I and II. The results are now added. The need for additional characterisation remains. The SCHEER agrees that menthol cigarettes per se are not more toxic than menthol-free cigarettes. However, indirect toxicity was established (see also Opinion I): adequate data indicate that

			a robust prediction of the compounds that are formed from additives during cigarette smoking studies.	menthol presence is associated with increased smoking initiation and greater addiction, especially among young people, as confirmed later by the studies of Nonnemaker et al. (2013) and Brennan et al. (2015).
145.	Ureel, Ludwig, British American Tobacco, Ludwig_Ureel @bat.com, United Kingdom	2.5.12 Menthol	Pyrolysis studies conducted under conditions which simulated those of a burning cigarette [4] demonstrate that 99.0% of menthol would be transferred into the mainstream smoke intact. Contrary to the Opinion's statement that "pyrolysis of menthol may result in carcinogenic" substances [p.62:13-14], small amounts of pyrolytic breakdown products were identified, none of which were carcinogens. Further studies [1] [2] [3], in which menthol was included in a test cigarette at 2.34%, and compared to an additive free control product, have confirmed that the mainstream smoke yields were not increased, and that the majority of constituents were reduced by the presence of the additives. The Opinion claims that menthol "impacts youth initiation" "contributes to adults continuing to smoke" and "has an adverse impact on public health by increasing the numbers of smokers with resulting premature death and avoidable morbidity" as well as the suggestion that "removal of menthol cigarettes from the marketplace would benefit public health in the United States" should be withdrawn (p.61:14-19). However, such claims are based on the TPSAC 2011 report which was "irrevocably tainted" and described as "at a minimum, suspect, and, at worst, untrustworthy" due to a conflict of interest [57]. Furthermore, these claims do not concern any of the Article 6 TPD2 criteria, and so are beyond the Terms of Reference of the Opinion.	The pyrolysis results of Baker & Bishop and others were accidentally not included in Opinion I and II. The results are now added. The need for additional characterisation remains. The evidence available is considered convincing enough. Secondary sources of information used as evaluations carried out by other Agencies (i.e. EFSA or US-EPA) were considered fully reliable. The same for the additives evaluated by the PITOC project WG: the information included in the fact-sheet was compiled following an extensive literature search and evaluation up to 2012. More recent data was added by the SCENIHR. The documents on the ruling are not very convincing. FDA did not find any conflict of interest. FDA disagreed with the ruling, but had no other option than to comply and replace the experts concerned. It is true that according to US law the 2011 report could not be used by FDA, but that does not, in the opinion of the SCHEER, disqualify the content. Moreover, the recent WHO Advisory (2016) says: "the tobacco industry challenged the composition of the TPSAC, which resulted in a legal decision that three members

				of the Advisory Council should be precluded from participating in the panel because they were expert witnesses in tobacco-related litigation, which was ruled to be a violation of conflict of interest provisions. As a result, the FDA could not use any of the conclusions in the TPSAC (2011) report. The ruling has been appealed; a final decision has yet to be issued. The SCHEER agrees that menthol cigarettes per se are not more toxic than menthol-free cigarettes. However, indirect toxicity was established (see also Opinion I): adequate data indicate that menthol presence is associated with increased smoking initiation and greater addiction, especially among young people, as confirmed later by the studies of Nonnemaker et al. (2013) and Brennan et al. (2015).
			The recent FDA report on menthol [41] is relevant to the Article 6 TPD2 criteria. This report suggests that menthol in cigarettes has minimal effect on toxicological properties of cigarette smoke or on smokers' exposure to tar and toxicants, and that menthol in cigarettes is not associated with an increase in disease risk to the user compared to non-menthol cigarette smokers. Furthermore, there is no consensus that menthol adds to the addictiveness of cigarette smoking.	
146.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.12 Menthol	Page 61, Lines 1-38 Although it is widely reported in the literature that menthol produces a local anaesthetic effect, this claim is not supported by mechanistic scientific evidence. A study by Galeotti et al., (2001) suggested that exposure to menthol attenuates muscle contractions, but did not demonstrate menthol's ability to block action potentials of nerves and more specifically to block ion movement through Na+ channels of these nerves as an anaesthetic. Several investigators have provided mechanistic evidence that menthol does not block action potentials in nerves (Swandulla et al., 1987) and that menthol is not a potent inhibitor of Na+ channels (Haeseler et al., 2002). In summary, menthol does not act as an anaesthetic. There is no evidence of increased biomarker exposure to menthol cigarettes (Heck 2009). Concerns over the use of menthol in cigarettes are	The evidence available is considered convincing enough. Secondary sources of information used as evaluations carried out by other Agencies (i.e. EFSA or US-EPA) were considered fully reliable. The same for the additives evaluated by the PITOC project: the information included in the fact-sheet was compiled following an extensive literature search and evaluation up to 2012. More recent data was added by the SCHENIHR. The literature cited was not considered convincing enough to lead to changes in the Opinion. The SCHEER agrees that menthol cigarettes per se are not more toxic than menthol-free cigarettes. However, indirect toxicity was established (see also Opinion I): adequate data indicate that

			that they may enhance the toxicity and smoking related health effects when compare to non-mentholated cigarettes. The collective body of scientific evidence demonstrates that: • Menthol cigarettes do not result in increased toxicity in non-clinical toxicity testing when compared to non-mentholated cigarettes • Smoking menthol cigarettes produces no consistent effects on the exposure to cigarette smoke (Strasser et al., 2013) • Smoking mentholated cigarettes produces no consistent changes in effects on human puffing and inhalation behaviour • Epidemiological evidence does not suggest any effect of mentholation of cigarettes having an effect on disease risk (Blot et al., 2011) • Scientific evidence does not support a role for menthol in the smoking related disparities seen between white and African American smokers In summary, the weight of the scientific evidence clearly demonstrates that there are no significant differences in health outcomes between menthol smokers and smokers of non-menthol products. Page 61, Lines 1-13: These are a series of hypotheses of possible actions of menthol. These hypotheses have contradictory studies available in the scientific literature. There are no citations for any of the statements made. These studies should form part of a systematic weight of evidence approach which includes reference to comparative toxicology and takes both positive and negative studies in to consideration. We support evidence based on robust methods and credible scientific research, on which valid assessment can be based.	menthol presence is associated with increased smoking initiation and greater addiction, especially among young people, as confirmed later by the studies of Nonnemaker et al. (2013) and Brennan et al. (2015). See previous answers on the same topic (e.g. comment n°144).

			Page 62, Lines 13-16: We agree with SCHEER that no validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative the conditions required for the intended use, whereby additives are combusted with tobacco, a point clearly recognized within Art. 6.3 of the Directive. Menthol sublimes at room temperature and has a boiling point of 212oC, and therefore transfers intact at 99% (Baker et al., 2004). Pyrolysis studies are unnecessary, as those already done demonstrate that menthol is not pyrolysed within a burning cigarette. Page 62, Lines 39-41: These results are not supported by human studies. In humans, no differences in biomarkers of exposure have been reported (Heck 2009, Industry menthol report 2011). The weight of the scientific evidence clearly demonstrates that there are no significant differences in health outcomes between menthol smokers and smokers of non-menthol products	Thank you for your comment. The pyrolysis results of Baker & Bishop and others were accidentally not included in Opinion I and II. The results are now added. The need for additional characterisation remains. See the previous answers.
147.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.12 Menthol	SCHEER is relying on SCENIHR's "rational for inclusion" for menthol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)" (comment to 3.3.20 Menthol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a relevant criterion under Art. 6 and Art. 7 TPD, we suggest to delete "or does	The evidence available is considered convincing enough. Secondary sources of information used as evaluations carried out by other Agencies (i.e. EFSA or US-EPA) were considered fully reliable. The same for the additives evaluated by the PITOC project WG: the information included in the fact-sheet was compiled following an extensive literature search and evaluation up to 2012. More recent data was added by the SCENIHR. The word attractiveness has been replaced.

			or does not increase attractiveness" on p. 62, l. 21.	
148.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.13 Propylene glycol	p.62, l.33-39 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Only taste and smell are considered in the definition for characterizing flavor provided by the TPD2. According to Article 7 (1), "'characterising flavour' means a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. p.62, l. 37-39 This sentence should be removed as it is inconsistent with SCHENIHR Opinion 1, which mentioned that "Propylene glycol does not have a strong flavour, and is, therefore, not expected to impart a noticeable flavour." To our knowledge, no additional information has altered this conclusion. P.63, l.6-9 Propylene oxide has been identified in the mainstream smoke of cigarettes with and without propylene glycol added (Klus et al., 2012; Diekmann et al., 2006). While the yield of propylene oxide increases with increasing propylene glycol application level in research cigarettes, propylene oxide is also detected in additive free control cigarettes suggesting either natural occurring	The word attractiveness has been replaced. This has been removed. This sentence has been removed. This paragraph has been taken from the previous Opinion (Opinion 1; rational for inclusion). The following paragraph within the rational for inclusion acknowledged the complexity of the mixtures in cigarette smoke. As propylene oxide is found and this increases with increased propylene application it is important to keep this sentence in.

			propylene glycol in tobacco or other precursors as source for formation (Heck et al., 2002).	
			p. 63, l.19 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed.	The text has been changed to address this comment.
			p.63, l.17-20 Please refer to recent inhalation studies with mainstream smoke of research cigarettes. (Heck JD et al., 2002, Gaworski CL et al., 2010) The results indicate that the addition of propylene glycol to cigarette tobacco and design at levels resembling or exceeding typical commercial application rates does not substantially alter the incidence, distribution, or severity of biological effects normally seen in the respiratory tract tissues of rodents after cigarette smoke exposure. This approach is consistent with the TPD2 requirement, Article 6(2) (a), (d) and Article 7(9), to test under the condition of use.	This information could be presented by the TI together with all the available studies (Step 1 and 2) for the MS assessors to evaluate them on the basis of a WoE approach, considering their relevance.
			p.63, l.21-22 Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not	See previous responses to this same issue.

			be used for a quantitative measurement. p.63, l.27-28. It is unclear why glycerol is mentioned in the "propylene glycol" section.	The typo has been corrected in the text.
149.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.13 Propylene glycol	All propylene glycol used by BAT is either food, or pharmaceutical grade, and so meets the purity requirements of E1520, as defined in COMMISSION REGULATION (EU) No 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council or the current United States and/or European (USP/EP) pharmacopoeias. This is to ensure that levels of residual solvent and heavy metal contamination are minimised, and that the necessary microbiological criteria are met. The of Margin of Exposure ("MOE") assessment described in the Opinion (p.63:2-5) has over complicated the exposure scenario by trying to estimate continuous alveolar concentrations, and fails to consider a more realistic intermittent smoke exposure (i.e. puff by puff, cigarette by cigarette). Moreover, it is important to note that MOE is not a direct measure of risk [32], and so these recommended tests fail to provide an outcome that is relevant to tobacco smoking. Pyrolysis studies conducted under conditions which simulated those of a burning cigarette [4] demonstrate that 86.3% of the propylene glycol would be transferred into the mainstream smoke intact. Whilst other pyrolytic breakdown products were identified, none of these were propylene oxide, which is attributable to the trace amounts permitted in either food or pharmaceutical grade propylene glycol. The Opinion suggests that interactions between propylene glycol, its breakdown products, and the	Noted. Please see previous answers on the same issue (Pyrolysis studies and CT).

			other components of smoke need to be considered. However, earlier publications in which mixtures of additives were tested, address potential additive effect or interactions between compounds [1], [2], [3]. Furthermore, extensive studies have shown that the use of propylene glycol as a tobacco ingredient at typical application does not increase the toxicity of cigarette smoke. BAT's own studies have shown that whilst the addition of high levels of propylene glycol (up to 8.3%) has a minor impact on the composition of mainstream smoke, it had no effect on the results of either in vitro or in vivo toxicity studies, when compared to a control product [1], [2], [3]. The findings of these studies are consistent with other data sets also available in the public domain. Propylene glycol is an active ingredient in the solutions used to generate synthetic smoke – widely used in nightclubs and the performing arts – it has been thoroughly evaluated and is considered safe by the Royal college of Physicians [74].	This information provided in paragraphs 2 to 5 (response 149) could be presented by the TI together with all the available studies (Step 1 and 2) for the MS assessors to evaluate them on the basis of a WoE approach, considering their relevance. This is outside of the scope of the current Opinion.
150.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.13 Propylene glycol	Page 63, Lines 14-16: Please note that Imperial Tobacco Ltd uses Pharmacopeia grade propylene glycol with a high purity. Page 63, Lines 17-20: Recently, the German Federal Institute for Occupational Safety and Health submitted to the European Chemical Agency ("ECHA") a proposal for Harmonized Classification and Labelling (CLH dossier dated October 2015) of Propylene Glycol as STOT SE 3, with the hazard phrase H335: May	Noted.

			cause respiratory irritation. This proposal cited human and in vivo studies, which they claimed to show evidence of propylene glycol causing respiratory irritation. However, we recommend that SCHEER exercises caution with the interpretation of these assays, as they have methodological flaws or suffer from inconsistent / inconclusive results. Page 63, Lines 21-22: The pyrolytic behaviour of propylene glycol has been studied by Purkis et al,. (2011), and showed that 99.4% of this compound transfers intact into mainstream smoke. Page 63, Lines 23-24: We would request that SCHEER provides a list of validated in silico / vitro assays which can assess if propylene glycol facilitates cigarette smoke inhalation. Page 63, Lines 24-26: The behaviour of propylene glycol in a cigarette with a complex mixture of additives has already been investigated by Baker et al., (2004), Carmines et al., (2002), Gaworski et al., (2010) and Heck et al., (2002). Propylene glycol was not observed to significantly change the biological activity of the smoke in these studies. Page 63, Lines 27-28: There appears to be a typographical error in this section of the report, as the authors refer to "the systemic effects of glycerol". If this statement was meant to apply to propylene glycol, SCHEER will be interested to note that Propylene glycol has been approved for use as a food additive by JECFA, with an Acceptable Daily	It is not the SCHEER's remit to assess proposals submitted to ECHA and it is not within the scope of this Opinion to assess this dossier. This question is outside the scope of the Opinion and the remit of the SCHEER. The text has been corrected.

			Intake of 25mg/kg BW/day. This additive has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints). ECHA makes this information publicly available on its website: http://echa.europa.eu/. We would request that SCHEER provides a list of validated in silico / vitro assays which can thoroughly assess the systemic effects of propylene glycol.	This request is outside the scope of the Opinion and the remit of the SCHEER.
151.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.13 Propylene glycol	SCHEER is relying on SCENIHR's "rational for inclusion" for propylene glycol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)" (comment to 3.3.24 Propylene glycol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of the SCHEER's mandate, it should be deleted in the sentence on p. 62, l. 33-34. We suggest the amended sentence be "Humectants are added to trap water, thereby keeping the moisture in the tobacco and preventing it from drying out." For the same reason, the sentence "Propylene glycol is (…) noticeable flavour" (p. 62, l. 37-39) should also be deleted. Furthermore, we suggest to remove the section on attractiveness in the sentence on p. 63 l. 17 – 20	Sentence has been changed to address this comment. This sentence has not been modified again as it was already changed to leave out the reference to attractiveness. The sentence has been changed accordingly.

			and suggest the amended sentence be: "Data available should be collected to prove or disprove whether propylene glycol increases the risks of effects on the respiratory tract epithelium."	
152.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.14 Sorbitol	p. 63, l. 34-37: Please remove the reference to "Attractiveness" as it is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. p. 64, l.2-5: Please replace "are inconclusive" by "has no evidence". In its report on the addictiveness and attractiveness of tobacco additives, SCENIHR (2010) concluded that "there is little scientific evidence that acetaldehyde present in tobacco or tobacco smoke and produced by sugar pyrolysis is responsible for an increased addictiveness of nicotine through an inhibition of monoamine oxidases. … Although acetaldehyde is formed in tobacco smoke from sugar combustion, we agree that it is not demonstrated that acetaldehyde in tobacco smoke enters the brain through the smoke inhaled." Also, "A Dutch Ministry of Health Review RIVM report concludes that "[a]cetaldehyde is suspected to be involved in smoke and alcohol addiction. It is unlikely that acetaldehyde from cigarette smoke has direct reinforcing properties in man because there is no evidence that acetaldehyde from smoke reaches the brain since a comparison between smokers and non-smokers showed no difference in blood acetaldehyde levels." p.64, l.6-11 Please mention that when adding sorbitol or a mixture of sorbitol and sugars to experimental cigarettes, furfural levels were not increased compared to an additive free reference	Sometimes, the SCHEER used the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". This is already addressed by the careful wording used. In addition, since 2010 many new publications have been published on the topic of mono-amine inhibition contribution to addictiveness. Please see the replies to the previous comments on pyrolysis and comparative testing.

			cigarette (Baker & Bishop, 2005). This example shows that the pyrolysis technique tends to overestimate the amount of decomposition that non-volatile additives undergo relative to their behavior in a burning cigarette. In the case of sugars, large over-estimates of pyrolysis products have been documented (Baker & Bishop, 2005). In addition, the toxicity of cigarette mainstream smoke has been investigated by comparing additive free control cigarette and test cigarette containing sorbitol (Coggins 2011a). In vitro cytotoxicity and mutagenicity were not affected by added sorbitol. No consistent effects were observed in a 90-days inhalation study between control and test cigarettes. (Coggins et al, 2011a; Gaworski et al., 2011, Baker et al. 2004c) Therefore, please consider these findings in the final report. l.16-20: Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement. The guidance provided by SCHEER goes beyond requirements as defined in of the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive	Please see the replies to the previous comments on pyrolysis and comparative testing.

			results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation.	
153.	Ureel, Ludwig, British American Tobacco, Ludwig_ureel @bat.com, United Kingdom	2.5.14 Sorbitol	Pyrolysis studies, in conditions simulating those of a burning cigarette [4], have shown that whilst sorbitol breaks down into a number of constituents, no acrolein, acetaldehyde or formaldehyde is detected. These results contradict the data reported in the Opinion. It is important to note that the largest source of acetaldehyde in cigarette smoke comes from tobacco pyrolysis and combustion. We note that the Opinion suggests that interactions between sorbitol, and its breakdown products, and the other components of smoke need to be considered [p.64:12-14]. BAT has published a number of papers in peer reviewed journals, in which mixtures of additives were tested, and the results of which are consistent with other extensive data sets also available in the public domain. This data also addresses possible additive effects. Studies in which sorbitol was included in a test cigarette at 3.53%, and compared to an additive free control product, confirmed that the mainstream smoke yields were not increased by the presence of the additives, and indicate that there is no greater toxicological effect from cigarettes containing 3.53% sorbitol when compared to those without. [1], [2], [3] The assertion that aldehydes formed during combustion potentiate nicotine addiction is not scientifically proven and does not take into account available scientific knowledge. As previously reported by SCENIHR [44], very few studies have	Especially if data appear to be inconclusive, the SCHEER concluded that additional pyrolysis studies are needed. It is irrelevant here whether or not most of the acetaldehyde results from natural tobacco components, as the current Opinion is on the contribution of additives to toxicity and addictiveness. Please see the general statement on pyrolysis and comparative testing. This is already addressed by the careful wording used: data are inconclusive. Note that acetaldehyde is a very reactive component.

			been able to identify acetaldehyde in the blood of smokers. Those that have only find it in very small and biologically insignificant concentrations, i.e. below those required to exert an effect in the brain. Whilst animal studies have indicated that aldehydes increase nicotine self-administration, such studies have involved the injection of large amounts of aldehydes, many orders of magnitude higher than those reached in the blood of smokers [44]. It should also be noted that the 2010 SCENIHR report dismissed the potential for aldehydes in potentiating addiction, suggesting "no (indirect) addictive effect of sugars when used as a tobacco additive" and that due to its exhalation "it is uncertain whether the acetaldehyde in smoke contributes significantly to the blood level of this substance" [44].	
154.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.14 Sorbitol	Page 64, Lines 6-11 & 16-22: SCHEER should note that Baker and Bishop (2005) performed a follow up test, adding 3.5% (by weight) sorbitol to a cigarette and determining its effect on smoke furfural levels. No significant differences in furfural levels were observed between control and test cigarettes. Overall, Baker and Bishop (2005) concluded that "in this case the pyrolysis result is a false positive". They also went onto conclude that "this indicates again that the pyrolysis technique is not suitable for predicting the behaviour of involatile substances in a burning cigarette". SCHEER should be made aware that there are various studies in the public literature which assess the behaviour of Sorbitol in a combusted cigarette and its biological effects (Baker et al., (2004) and Gaworski et al., (2011) at levels several magnitudes higher than what are traditionally used for	Please see the general statement on pyrolysis and comparative testing.

			commercial cigarettes. No significant differences between control and test cigarettes were observed in any of these studies.	
155.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.14 Sorbitol	SCHEER is relying on SCENIHR's "rational for inclusion" for sorbitol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)" (comment to 3.3.25 Sorbitol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, it should be deleted in the section on p. 63, l. 34 – 39. We suggest the amended text be "Humectants are added to trap water, thereby keeping the moisture in the tobacco and preventing it from drying out. Sorbitol is, therefore, considered to influence cigarette smoking given that humidification improves palatability of cigarettes. Sorbitol gives tobacco smoke a slightly bitter taste and a vague odour of cellulose and is, therefore, not expected to impart a noticeable flavour when used in higher amounts." Furthermore on p. 64, l. 25 we also suggest to delete the term "that is attractive." As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 6(2), (3) and Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to amend p. 64, l. 19 - 22 as follows: "In case of positive results, additional testing would	See the answer to comment 152. See our previous answer on the same topic.

			be necessary to generate additional data for a Weight of Evidence assessment."	
156.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.5.14 Sorbitol	*Repetition of comment Nr 11*	Please see the answer to comment n°11.
157.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.5.14 Sorbitol	*Repetition of comment Nr 11*	Please see the answer to comment n°11.
158.	Vizée, Huub, delfortgroup, huub.vizee@delfortgroup.com, Austria	2.5.15 Titanium Dioxide	2.5.15 Titanium Dioxide CAS numbers: 13463-67-7 (mixture of mainly rutile and anatase); 1317-80-2 27 (rutile); 1317-70-0 (anatase) Opinion II states that "both nano and non-nano-size titanium dioxide were classified by IARC as a Group 2B carcinogen (i.e. possibly carcinogenic to humans) (IARC, 2010)". However; the IARC classification reads differently. Nano-size TiO2, contrary to micro-size TiO2, was classified in the 2B group by the International Agency for Research on Cancer (IARC). IARC states that there is inadequate evidence in humans for the carcinogenicity of nano-size titanium dioxide, that there is sufficient evidence in experimental animals for the carcinogenicity of nano-size titanium dioxide and therefore the Working Group from IARC considered that the available mechanistic evidence for nano-	Thank you for pointing this out. IARC indeed does not make a distinction with respect to particle form or size. The text is adapted accordingly. However, no analytical data have been provided to clarify the particle size of TiO_2 in cigarettes.

			size titanium dioxide was not strong enough to warrant a classification other than Group 2B. Nano particles are $1 < \varphi \leq 100$ nm in size and the particle size of titanium dioxide used for the production of Tipping Paper is > 100 nm and therefore not classified in Group 2B from IARC. Therefor SCHEER's proposal to study nano-size titanium dioxide doesn't make any sense. On top of that SCHEER suggests to determine the amount of titanium dioxide in mainstream smoke as in subacute repeated dose inhalation toxicity studies, nano-size TiO2 induces an acute inflammation in the lungs. However; micro-size titanium dioxide is only used for tipping paper, not being combusted when used, which means that the used micro-size titanium dioxide is enclosed at one side by the printing of the tipping paper and at the other side by the plug wrap paper (between tipping paper and filter). Therefore it is impossible for the micro-size titanium dioxide to enter the mainstream smoke. SCHEER therefor has two wrong assumptions which did lead to the proposal to investigate titanium dioxide and based on above it can be concluded that the used micro-size titanium dioxide has no CRM properties in unburnt form and it does not increase to a significant or measureable degree the addictiveness, toxicity or the CMR properties of the tobacco product as it does not enter the mainstream smoke. Titanium dioxide should therefore be taken from the list.	The frequency of detection of TiO_2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which 1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive 2001/37/EC). The difference of 73 occurrences has not been explained by the tobacco industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke.
159.	Martinez, Javier, JT International SA, 8 rue Kazem	2.5.15 Titanium Dioxide	p. 64, l. 37-41 Please mention that there is currently no scientific evidence that suggests exposure of consumers to TiO2 from airborne, unbound and respirable size particles from filter tow	This may be true, but the frequency of detection of TiO2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which 1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive 2001/37/EC). The difference

	Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other		used in cigarette filters or from filter tipping paper.	of 73 occurrences has not been explained by the Tobacco Industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke.
160.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.15 Titanium Dioxide	Page 64, Lines 37-40: Titanium dioxide is used in logo inks (held in a matrix by varnishes), for tipping papers, and used in filters, none of which are burnt, unlike the tobacco rod. Under burning conditions, the melting point of titanium dioxide is over 1800°C, whilst its boiling point is almost 3000°C, these temperatures are not reached during combustion of a cigarette (Baker 1975). Typical cigarette temperatures in the burning zone reach 900oC. Therefore, even if it was used in tobacco the temperature is not high enough to oxidise, melt, nor volatilise the titanium dioxide, which would remain a solid and therefore remain in the cigarette ash. Hence it has not been reported in mainstream smoke. Page 64, Lines 40-41: As stated in preliminary opinion 1, the average particle size for titanium dioxide particles in the printing ink matrix is reported to be 300 nm (well above the EU commission range of 1-100 nm in any direction to be considered a nano-particle (2011/696/EU). Page 65, Lines 10-15: Titanium dioxide has been proposed in the dossier submitted by ANSES on behalf of the French Member State to reclassify titanium dioxide as a carcinogen category 1B, with a single classification	The frequency of detection of TiO_2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which 1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive 2001/37/EC). The difference of 73 occurrences has not been explained by the Tobacco Industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke. Opinion 1 does not report on the particle size. No analytical data have been provided to clarify the particle size of TiO_2 in cigarettes. The text is slightly adapted: "It is proposed to reclassify TiO2 (all forms). .". The current text is clear about the draft status of the proposal.

			of all forms of titanium dioxide. ECHA are still reviewing the comments. Both epidemiological data in exposed humans and non-rat animal studies indicate that titanium dioxide is not a carcinogen in non-rat species, and that any effects observed in rat studies are related to secondary mechanisms due to lung overload in the rat, (genotoxicity via ROS formation due to lung bio persistence of the particles). The rat is known for its particular pulmonary sensitivity when compared to humans and other animals (rodent and non-rodent species). The bio persistence in the rat has been linked to the different functional anatomy of the lungs of rats and humans. The location of the particulate matter accumulation in the lungs of rats is essentially different to that of humans, with the majority of similar sized non-soluble diesel particles in rats (up to 85%) being located in the alveolar and alveolar duct lumens and up to 91% of particulate matter in coal miners being located in the interstitium of the lungs. The ECETOC report (2013) discusses the rat model as being particularly sensitive to the development of pathological responses in the lung, and that these responses are not seen in other rodent models such as mouse or hamster. There is a lack of response in humans for PMNs (polymorphic neutrophils) in high dust exposed workers. PMNs are a critical part of the inflammatory response in the rat. The BALF biomarkers in human coal dust exposed workers corroborates the lack of carcinogenic response in the epidemiological data seen in humans (Morfeld et al., 2015).	Thank you for this opinion on the carcinogenicity of TiO_2. The WG did not re-evaluate this issue and instead relied on current evaluations by international bodies like IARC and ECHA. It is requested that uncertainties be clarified on the basis of international research.
161.	Ureel, Ludwig, British	2.5.15 Titanium	Titanium dioxide, which is used as a filler in a cigarette paper, is bound in the cellulosic structure	The frequency of detection of TiO2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which

	American Tobacco, ludwig_ureel @bat.com, United Kingdom	Dioxide	of the paper. It has a melting point of over 1800°C, and a boiling point of almost 3000°C. Accordingly, when heated in a burning cigarette it does not oxidise, melt, or volatilise. It remains a solid and so ends up in the cigarette ash. Titanium dioxide is classified as an IARC Class 2B human carcinogen [45]. However, this classification is associated with experimental animal exposure to high concentrations of titanium dioxide dust, and has not been seen in human epidemiological studies. In fact, the effects of "lung overload" in rats (which follows a well characterised mechanism of particle deposition, followed by impaired clearance and accumulation of particles in the lung, causing inflammation, cell injury, fibrosis, production of reactive oxygen species that eventually lead to mutations, and ultimately cancer) are a well-recognised response to exposure to many other dusts, including carbon black [46] which is also classified as a 2B carcinogen by IARC. Therefore the relevance of the IARC classification to the use of titanium dioxide in cigarettes is questionable. Furthermore, regarding the proposed reclassification under CLP, the available data used as evidence in the dossier submitted by ANSES on behalf of France does not support the proposed classification of titanium dioxide as a carcinogen category 1B, nor does it support a single classification of all forms of titanium dioxide. Conversely, both epidemiological data and non-rat animal studies indicate that titanium dioxide is not a carcinogen and that any effects observed in rat	1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive 2001/37/EC). The difference of 73 occurrences has not been explained by the tobacco industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke. Thank you for this opinion on the carcinogenicity of TiO_2. The WG did not re-evaluate this issue and instead relied on current evaluations by international bodies like IARC and ECHA. It is requested that uncertainties be clarified on the basis of international research.

			studies are related to secondary mechanisms due to "lung overload" in the rat. Rats are susceptible to particular pulmonary sensitivity compared to humans and other animals (rodent and non-rodent species).	
162.	No agreement to disclose personal data	2.5.15 Titanium Dioxide	In the papers included in a cigarette, titanium dioxide is used in the tipping base paper and in the inks used to print it. According the conclusions of the Preliminary Opinion II on Tobacco Additives, for titanium dioxide research is needed to determine the amount of titanium dioxide in mainstream cigarette smoke. Because inhalation toxicity is also related to the size of the particles, a distinction needs to be made between nano and non-nano size. First point to be clarified is the difference between nano and no-nano materials. According the definition of the REGULATION (EC) No 1223/2009, article 2 – 1 (k) and Commission Recommendation 696/2011, 'nanomaterial' means an insoluble or biopersistant and intentionally manufactured material with one or more external dimensions, or an internal structure, on the scale from 1 to 100 nm. The titanium dioxide used in the paper industry has a particle size average between 0,20 and 0,35 microns (200 to 350 nanometers) and this measurement depends on the system used. Moreover, in practice, the particles trend to agglomerate in the micron area. Additionally, the base tipping paper and its printed area are not burned during the smoking of a cigarette and have no direct contact with the	According to the recommendation the exact definition is: A natural, incidental or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50 % or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm - 100 nm. In specific cases and where warranted by concerns for the environment, health, safety or competitiveness, the number size distribution threshold of 50% may be replaced by a threshold between 1 and 50%. It is noted that no analytical reports have been provided to clarify the particle size of TiO_2 in cigarettes. The frequency of detection of TiO_2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which 1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive

			smoke, and in both cases, the titanium dioxide particles are retained by the cellulosic fibers in the case of the base paper and by the printing binder in the case of the printed layer, so it is difficult to see a way to get titanium dioxide particles in the smoke stream.	2001/37/EC). The difference of 73 occurrences has not been explained by the Tobacco Industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke.
163.	Westgeest, Alfons, GAMA, gama@kellen europe.com, Other	2.5.15 Titanium Dioxide	page 64: line 37-41 page 65: line 1-22 Titanium dioxide (TiO2) is used by GAMA's members at relatively low levels as a delustering agent in the production of cellulose acetate tow and cellulose acetate yarn. Cellulose acetate tow is then used in the manufacturing of cigarette filters. The filter material is not intended to be combusted during normal use. Cellulose acetate yarn is a fiber used in various textile applications, such as apparel. Over the past 50 years GAMA members have safely used titanium dioxide in their production processes. Titanium dioxide has unique refractive properties in these applications to which there are currently neither economic nor functionally viable alternatives available. GAMA believes that titanium dioxide should not be re-classified as "potentially carcinogenic to humans" (category 1B) / "may cause cancer by inhalation" (H350i). GAMA also believes that titanium dioxide does not meet the carcinogenic criteria as set out in the Classification, Labelling and Packaging regulation ((EC) No 1272/2008).	The frequency of detection of TiO_2 in different brands was given as 1329 in Table 2 of Opinion 1 on Tobacco Additives of which 1256 occurrences in non-tobacco materials (data reported by the industry in the context of ingredient reporting under Directive 2001/37/EC). The difference of 73 occurrences has not been explained by the Tobacco Industry and therefore it is not clear whether TiO_2 is also present in tobacco and can be present in mainstream smoke. Thank you for this opinion on the carcinogenicity of TiO_2. The WG did not re-evaluate this issue and instead relied on current evaluations by international bodies like IARC and ECHA. It is requested that uncertainties be clarified on the basis of international research.

			 GAMA_statement_to _SCHEER_2016.pdf	
164.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.2 Cocoa and cocoa products (powder, extracts, shells of cocoa bean etc.)	The Opinion claims that the effects of cocoa on the toxicity of smoke, and the risk associated with the generation of combustion products have not been studied. This disregards the large number of peer-reviewed publications by the tobacco industry, including those from BAT [1] [2] [3] which have demonstrated that in biological studies under conditions of use, c**i**garettes containing additives, including cocoa products, have no greater toxicological effect than those without. For example, during cigarette combustion, groups of tobacco additives, including cocoa, at an application level of 3.7%, either reduced, or had no effect on the levels of most of the measured smoke constituents, nor did they have any impact on the results of in vitro studies, when compared to a control product. The findings of these studies are consistent with other extensive data sets also available in the public domain. Studies carried out by BAT have demonstrated that under conditions which simulated those of a burning cigarette [5] (cocoa breaks down, but that many compounds which SCHEER shows concern over are minor constituents of the pyrolysate. Furthermore, when cocoa was included in test cigarettes, and compared to an additive free control product, the mainstream yields of these constituents were not increased [1] [2] [3] As stated in the Opinion, exposure to theobromine	Comparative Testing (CT) of an additive in the tobacco matrix compared to the tobacco matrix without the additive is the only way to comply with Art.6TPD2 (A6) to assess whether additives <u>increase</u> "toxicity or addictiveness . . . to a significant or measurable degree". However, as the SCHEER clearly stated in the preliminary Opinion, the high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough become available, they could be used. The SCHEER indeed stated in the preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless and not in line with the intentions of article 6.2. Please see the response to the comment 1 for more details. See the comment above. On p.49, l.39: only scientific tests will be able to reveal whether

			in cigarettes seems too low to have a bronchodilatory effect on the lungs [p.49:39], and the doses required to exert such an effect in humans far exceed the levels present in cocoa as used as a tobacco additive. This is consistent with the SCENIHR 2010 report [44] (pg. 42). Furthermore, Opinion states that "Due to a lack of studies specifically directed to the psychoactive effects of cocoa compounds added to tobacco on addiction, there is insufficient evidence that the addition of cocoa to tobacco contributes to the addictive properties of cigarette smoking" (p.50:43). This is despite the conclusion of a number of reviews, including that by the RIVM [19], that "the individual level of the psychoactive compounds in cigarettes originating from cocoa does not increase the addiction to cigarette smoking". The statement "[b]ased on the available data, cocoa and cocoa products may increase attractiveness and addictiveness" is in contradiction to the statement that occurs but a few lines earlier that "there is insufficient evidence that adding cocoa makes cigarettes more addictive." The statement: "[c]hocolate flavour may make cigarettes more palatable to younger smokers" is an irrelevant statement unless it is demonstrated that cocoa on blend imparts a chocolate flavour to smoke when burnt, which it does not.	theobromine, alone or with other additives, in cigarettes induces a bronchodilator effect or not. On p.50, l.43: The same report cited makes the following conclusion: "However, the long-term local and systemic effects are not known of these compounds or their combustion products. The combustion products of some psychoactive compounds have MAO-I properties and those combustion products may contribute to the addiction to cigarette smoking." Therefore, there is uncertainty with regard to the psychoactive effects of cocoa compounds added to tobacco on addiction. The statement with "may increase" is not in contradiction with "insufficient evidence", because it indicates the probability and necessity of more data to confirm or exclude the effect of cocoa additives. The statement is based on RIVM: "Furthermore, the flavour of cocoa may act as a conditioned stimulus and the organoleptic properties of cocoa may be associated with dependency."
165.	Martinez, Javier, JT International SA, 8 rue Kazem	2.5.2 Cocoa and cocoa products (powder, extracts,	p.49, l.34-37 Please mention that tobacco smoke from test cigarettes containing cocoa at levels up to 44,000 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of	On p.49,l.34-37: the high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough become

	Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	shells of cocoa bean etc.)	the smoke was not altered by adding cocoa. (Carmines et al., & Rustemeier et al., 2002; Baker et al., 2004a,b; Coggins et al., 2011c; Gaworski et al., 2011., & Roemer et al., 2002; Baker et al., 2004c; Roemer et al, 2010 Gaworski et al., 1998; Vanscheeuwijck et al., 2002; Roemer and Hackenberg, 1990; Gaworski et al., 1999) p.50, l.10-11 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. Please remove the sentence "imparts a noticeable "flavor" as it is inconsistent with the TPD2. According to Article 7 (1), "'characterising flavour' means a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product".	available, they could be used. The SCHEER indeed stated in the preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. Please see the answer n°1 to comment n°1. On p.50, l.10-11: it has been replaced by "the properties facilitating inhalation and resulting in characterising flavour". The SCHEER disagree that the sentence "imparts a noticeable "flavour" as it is inconsistent with the TPD2. Cocoa additives are used to smooth and enhance tobacco flavour, to sweeten tobacco and to add its own characteristic flavour (tobacco documents).
166.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United	2.5.2 Cocoa and cocoa products (powder, extracts, shells of cocoa bean	Page 50, Lines 7-9: We agree with SCHEER; there is no evidence that adding cocoa to tobacco makes cigarettes more addictive.	On p.50, l.7-9: "insufficient evidence" is not synonymous with "no evidence".

	Kingdom	etc.)	Page 50, Lines 10-11: SCENIHR (2010) addressed the substantial limitations in assessing or measuring the "attractiveness" of a tobacco additive by highlighting an absence of suitable animal models and ethical concerns should human testing be involved. It is fair to conclude from these limitations that no appropriate or validated methodology exists for measuring "attractiveness" of a tobacco additive. Consequently, from a scientific perspective, it is not meaningful for defining a list of priority additives. Moreover, the term is not within the Mandate given to SCHEER since "attractiveness" per se fails established criteria for issue definition: it is lacking in any evidential foundation and is inherently uncertain and arbitrary within a scientific context.	On p.50, l. 10-11: "attractiveness" has been replaced by "Regarding the properties facilitating inhalation and resulting in characterising flavour, the addition of cocoa to tobacco is intended to enhance flavour."
			Page 50, lines 15-17: SCENIHR (2010) concluded that the level of theobromine and application rate of cocoa was too low for a bronchodilatory effect. By inserting the word "may", SCHEER adds an element of doubt not in the original SCENIHR statement. Additionally, unless one of the biological breakdown products of cocoa is nicotine, it is questionable how cocoa can boost nicotine content. The plausibility of this hypothesis is therefore questionable (Mueller et al., 2000).	On p.50, l.15-17: Now the sentence cites the original SCENIHR statement.
			Page 50, Lines 22-26: Tryptophan is one of the amino acids commonly found in all tobacco varieties (Rodgeman and Perfetti 2009), and therefore on a weight for weight basis significantly more tryptophan degradation products would be expected to come from tobacco combustion than from the addition of cocoa as a	On p.50, l.22-26: The data cited in this Opinion can be found in SCENIHR 2010.

			casing. In a study by Guillen-Casla et al., (2012) regarding L-tryptophan content of chocolate, the highest content of this amino acid (13.27–13.34 μg/g−1) was found in chocolate samples with the lowest cocoa content (70–85%), indicating the low levels tryptophan found in added cocoa. On this basis, a 1% cocoa content equates to 0.093 ug/cig of potential tryptophan. This level is substantially below pharmacological active levels In this Preliminary Opinion SCHEER outline several hypotheses, not validated by scientific evidence, and contradicting available research (Mueller et al., 2000). We support evidence based on robust methods and credible scientific research, on which valid assessment can be based. Being a non-volatile component of the casing, cocoa is known to degrade with minor amounts of various constituents formed Baker et al., (2005). When applied to cigarettes at 0.4, 1.1 and 2.2% of tobacco weight, there was found to be no effect on mainstream smoke analytes, no effects on cytotoxicity, or mainstream smoke in vitro mutagenicity when compared to control cigarettes without the additives (Roemer et al., 2010). Page 50, Lines 41-43: The addition of cocoa to the tobacco does not add a chocolate taste to cigarette smoke. This sentence is misleading.	The high toxic potential of the tobacco matrix itself means that any effect of a single additive on the toxicity, addictiveness or CMR properties of the matrix, **cannot be discriminated with the currently available methodology**. This means that once methodologies sensitive enough would be available they could be used. The SCHEER indeed stated in the preliminary Opinion: *Very sensitive tests would be required, with a clear dose-response relationship, in order to show any differences from these high background effects. As such tests are not currently available, no comparative studies (tobacco product with and without additives) will be considered, since these studies lack discriminative power*. Thus, from a pragmatic point of view, this strict interpretation is meaningless, and not in line with the intentions of article 6.2. Please see the answer n°1 to comment n°1. On p.50, l.43, p.51, l. 2: changed to "characterising" flavour.

			Page 50, Line 43 - Page 51, Line 2: We agree, there is insufficient evidence that the addition of cocoa contributes to the addictive properties of cigarette smoking.	Thank you for your agreement.
167.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.2 Cocoa and cocoa products (powder, extracts, shells of cocoa bean etc.)	SCHEER is relying on SCENIHR's "rational for inclusion" for cocoa set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.10 Cocoa). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and 7 TPD nor part of SCHEER's mandate, we suggest to delete the sentence on p. 50, l. 10 and 11. Furthermore, on p. 50 l. 13 we also suggest to remove the term attractiveness. We propose to use the following sentence: "It has been suspected that cocoa and cocoa products may increase addictiveness and increase inhalation and nicotine uptake."	On p. 50, l. 10-11: the sentence has been changed. It now reads "Regarding the properties facilitating inhalation and resulting in characterising flavour, the addition of cocoa to tobacco is intended to enhance flavour." On p. 50, l. 13: the sentence has been changed. It now reads "Based on the available data, cocoa and cocoa products may facilitate inhalation, increase addictiveness and increase inhalation and nicotine uptake."
168.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.3 Diacetyl	Page 51, Lines 12-14: SCHEER should note that Diacetyl is a natural constituent of tobacco smoke. Fujioka et al., (2005) examined the mainstream smoke from 14 commercial brands of cigarette and one reference cigarette. Diacetyl was detected in the mainstream smoke of all the cigarettes tested at a range 301-411µg diacetyl per cigarette. SCHEER should also note that the mainstream smoke for two additive free cigarettes had 301µg and 331µg diacetyl per cigarette. The authors concluded that "…there were no significant differences in carbonyl compounds formation between cigarettes with and without	It is correct that diacetyl can be a natural constituent of tobacco smoke. Diacetyl is not in the list presented in the Scientific Opinion because it is a constituent of tobacco smoke but because it is used as an additive and because it is a potential hazardous compound.

			menthol or additives". Page 51, Lines 19-20: Diacetyl [FL-no: 07.052] was found able to induce gene mutations in S. typhimurium TA100 and TA104. Diacetyl was reported to produce mutations in the TK +/- locus of L5178Y mouse lymphoma cells. However, the concentration required for a two-fold increase in mutations results in a 62 % growth reduction, rendering this effect questionable (Whittaker et al., 2008). In an unpublished GLP study on in vivo micronucleus formation in B6C3F1mice diacetyl was reported negative, however, since the PCE/NCE ratio was not reported it is not clear whether the test substance reached the target organ (NTP, 1994c). With regards to the genotoxicity of Diacetyl, SCHEER should know that EFSA has already assessed this. In 2011, they concluded that "there is indication that diacetyl [FL-no: 07.052] has a weak genotoxic activity in vitro. However, diacetyl is reported to be endogenous in humans and is reported to be rapidly reduced to acetoin and further to butan-2,3-diol, for which there are no indication of mutagenicity". EFSA's findings are useful and should be considered in an update to the preliminary opinion. Page 51, Lines 21-32: Pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. SCHEER will be interested to note that a pyrolysis study has already been performed. Baker and Bishop (2004), observed that diacetyl transferred	It is correct that the genotoxicity of diacetyl is not fully explored and the presented data leaves open some uncertainty, therefore the compound is on the list of the scientific Opinion. The reference to the EFSA report is partly correct. The EFSA noted: '*There is indication that diacetyl [FL-no: 07.052] has a weak genotoxic activity in vitro. However, diacetyl is reported to be endogenous in humans and is reported to be rapidly reduced to acetoin and further to butan-2,3-diol, for which there are no indication of mutagenicity.'* Thus EFSA indicates that there is not a major concern for diactyl (when exposure takes place via indigestion), but the genotoxic character of the compound is recognised. In the context of smoking, the exposure route is different: oral data cannot simply be copied when inhalation is considered. For pyrolysis, see the SCHEER's response to comment n° 72. Thank you for the additional reference. It was added in the list of references.

			95.7% intact. Page 51, Lines 22-23 & 33-35: Traditional tobacco industry usage levels of Diacetyl have been reported as 15ppm (Baker et al., 2004). Pierce et al., (2014) have measured the mean diacetyl concentrations in mainstream smoke from 6 different cigarette brands and observed the levels ranged from 250 to 361 ppm for all tobacco products tested originating from the tobacco itself. The authors concluded that "…smoking has not been shown to be a risk factor for bronchiolitis obliterans". SCHEER should be aware that there are various studies in the public literature which assess the effects of diacetyl in tobacco following inhalation (Baker et al., (2004), Carmines et al., (2002), and Gaworski et al., (1998)) at levels several multitudes and in some cases magnitudes higher than what are used for commercial cigarettes. Even under these exaggerated inclusions, no significant differences between control and test cigarettes were observed in any of these studies. Page 51, Lines 24-27 & 33-35: That an additive in isolation may have a characteristic flavour above a specific level (perception threshold) does not result in it resulting in that same flavour in the tobacco product nor to creating a product with a characterising flavour. The SCENIHR report of 2010 concluded that current methods are not adequate for a reliable quantification of attractiveness or addictiveness of nicotine and tobacco additives. There are no validated studies of any kind on attractiveness which would substantiate SCHEER's call for an attractiveness assessment. Furthermore,	It is not clear what the author wants to express with this remark. It is correct that diacetyl is formed during burning, but it unclear what the link is with bronchiolitis obliterans. In the Opinion, mainly the potential genotoxicity of diacetyl has been discussed. For CT see the SCHEER's response to comment 1. Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". Regarding implementation of characterising flavour assessment, the SCHEER refers to this webpage of the European Commission: http://ec.europa.eu/health/tobacco/products/implementation/characterising_flavours_en.htm

			attractiveness does not fall within SCHEER's Mandate for this Preliminary Opinion 2.	
169.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.3 Diacetyl	PMI does not use diacetyl and will not carry out enhanced testing of the additive. Since attractiveness is not a relevant criterion under Art. 6 and 7 TPD, it should be deleted in the sentences on p. 51, l. 16 and l. 25 - 27.	The Opinion only refers to use of additives in general and not to specific brands. See also the answer to comment n°168.
170.	mirkova, ekaterina, e.mirkova@gmail.com, Bulgaria	2.5.3 Diacetyl	Paragraphs 12, 14, 19, 20, 33, page 51  Mirkova_Comments_ TobaccoAdditives_Dia	Thank you for the useful comments; they strengthen the SCHEER decision to include diacetyl in the list. Moreover the fact that SCOEL defined clear OEL levels is an important sign to look into this compound in more detail when it is used in consumer products.
171.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.4 Fenugreek extract	p.52, l.8-10 Experimental cigarettes containing Fenugreek did not exhibit increased smoke constituents levels when compared to an ingredient free reference cigarette (Carmines, 2002 & Rustemeier et al., 2002, Baker et al., 2004a) Tobacco smoke from test cigarettes containing fenugreek at levels up to 585 ppm and additive free reference cigarettes were tested in 90-day inhalation studies. In these studies, the biological activity of the smoke was not altered by adding fenugreek. Specifically we refer to the following publications: Gaworski et al., 1998; Carmines et al., & Vanscheeuwijck et al., 2002; Baker et al., 2004c. p.52, l.32-36 Please delete line 32- to 36. SCHEERS's referral to article 7 2a is incorrect, simply because article 7 2a does not exist in the	Please refer to the answer to comment 1 for a comprehensive explanation about the SCHEER reasoning on comparative testing and comment 26 (studies for submission). The SCHEER welcomes the fact that tobacco industry already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about comparative testing. Thank you for pointing out the typo, which has been corrected in the text to article 7 6 a. The text was also amended accordingly.

			TPD2. Nevertheless, SCHEER goes beyond its mandate as to interpret the TPD2. p.52, l.45 onwards SCHEER's coercive proposal to impose a burden of proof on manufacturers to prove that the "addictiveness" properties do not exist for any particular additive is inconsistent with the TPD2. Notably, article 6(2) and Article 7(9) simply require manufacturers to provide data on the properties of the relevant additives. Please retract the "burden of proof" constraint. p.53, l.2 It is crucial that the concept of "addictiveness" is adequately defined and that "addictiveness" is objectively measureable before it may be considered as a basis for regulation. 6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion. A scientifically valid approach to evaluating the dependence potential of a given additive is not available up to now.	Regarding addictiveness, please refer to the previous answer to the question on the same topic (addictiveness, 'burden of proof' consistency with the SCENIHR 2010 Opinion).
172.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.4 Fenugreek extract	Previous studies on the pyrolysis of fenugreek extract [5] yielded slightly different results from those described in the Opinion. No caramel colour, PAHs, formaldehyde, or pyrazines were produced. Instead, a complex mixture of pyrolysis products was identified. However, following additional investigations, it was concluded that none of the pyrolysis products added significantly to the levels of toxicants in smoke [2]. It is important to note that pyrolysis is likely to over predict the thermal breakdown of non-volatile compounds, and hence smoke chemistry should also be considered as part of ingredient assessment [61]. Despite the Opinion's claim that fenugreek extract is	Please see the answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission). The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. Changes made in the text for more clarity.

			predominantly sugar (in fact, it is less than 5% sugar) and will therefore produce large amounts of toxic compounds and compounds with CMR properties [p.52], previous studies on the effect of sugars directly have concluded that the presence of up to 10.5% sugar in a test cigarette did not increase the biological activity of the mainstream smoke [3]. Furthermore, the addition of up to 6.2% sugar, actually reduced the mainstream yield of furfural when compared to a control cigarette [5]. Based on these findings, it is unlikely that the addition of fenugreek extract, up to the levels used, will play a major role in the toxicity of tobacco products, despite the presence of sugar per se. During cigarette combustion, groups of tobacco ingredients, including fenugreek extract at 250ppm, generally had no effect on or reduced the levels of most of the measured smoke constituents, and levels of none were increased. Furthermore, these changes did not affect the smoke's in vitro cytotoxicity, in vitro bacterial mutagenicity, in vitro mammalian genotoxicity, or inhalation toxicity [3]. These results are consistent with other extensive data sets available in the public domain, and suggest that additives should be studied in comparative test cigarettes in accordance with the fact that their contributions to the smoke components are offset by the reduction in tobacco contributions. Article 7 TPD2 is beyond the scope of the Terms of Reference. Accordingly, SCHEER's statement that fenugreek "can thus give an impression of health benefit to the consumer, so could be considered under the TPD Article 7 2a" exceeds the Terms of Reference and therefore this Opinion. Moreover, this statement would only be credible if fenugreek extract were used in any consumer communication,	Please refer to the answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission) The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. Please see the previous answers to the same general topic. Wording has been changed whenever relevant to be consistent with the ToR and the TPD.

			which it is not. The opinion states that "the burden of proof is on the industry to use the proposed step-wise system (…) to prove that the additive is safe on all counts of toxicity, addictiveness and characterizing flavour in the unburnt and burnt form", this is not only making up obligations that do not exist under Article 6 of the TPD, but it also once again acts completely outside of the terms of reference.	
173.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.4 Fenugreek extract	Page 52, Lines 23-24: The evidence to date does not indicate the addition of fenugreek to cigarettes causes additional harm or contributes to the CMR properties of tobacco smoke to a significant and measurable degree (Carmines et al., 2002, Baker et al., 2004). Page 52, Lines 32-36: SCHEER should note that Coggins et al., (2011) assessed the smoke chemistry of cigarettes with added Fenugreek extract with a target inclusion level of 10,000ppm. Compared to a control cigarette with no test additive there were no statistically significant changes in smoke chemistry. No communications to this effect are made to our consumers. Additives may be added to tobacco products during manufacture. Additives (for example, flavourings typically used in food) are used in very small quantities in some brands to enhance their overall flavour characteristics and aroma, giving brand variants their own distinctive style, in line with consumer preferences. Additionally, due to the known health risks of smoking, we do not claim that tobacco products are "safe", neither do we make claims that any Tobacco Product is "safer" than another (unless endorsed and/or required to by regulatory authorities).	Please see the replies to answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission). The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. This is a general statement about the general population's perception. SCHEER was not accusing any company of explicitly communicating this type of message.

			Page 52, Lines 37-41: We agree with SCHEER that no validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, a point clearly recognized within Art. 6(3) of the Directive. Industry papers by Carmines (2002), Rustemeier et al. (2002), Roemer et al. (2002) and Vanscheeuwijck et al. (2002) The studies performed included a bacterial mutagenicity screen (Ames assay) a mammalian cell cytotoxicity assay (neutral red uptake), determination of smoke chemical constituents and a 90-day rat inhalation study. Based on the findings of these studies, the authors concluded that the addition of the combined ingredients, including fenugreek extract at levels up to 311 ppm, "did not increase the overall toxicity of cigarette smoke". Baker et al., [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The addition of fenugreek extract at 200 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, in vitro micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker et al., 2004]. Page 52, Line 45 & Page 53, Lines 1-3: We assess the appropriateness and acceptability of the additives we use. We employ a panel of experienced toxicologists to carry out studies on additives and to judge the suitability of these	Please see the general answer for the pyrolysis studies issue. Please see the answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission) SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER

			additives for inclusion in our products. It is requested that SCHEER provides a list of validated in silico / vitro assays which can thoroughly assess the neuropharmacological activities, CNS depressant/stimulant and allergenic properties of fenugreek extract.	indication about CT. This is outside the remit of the SCHEER mandate. The SCHEER was not asked to give detailed protocols but to advice the Commission on a possible framework to help the MS in asking and Tobacco Industry (TI) to present sound data; in particular the ToR states: *The Committee is asked to advise the Commission on the **type and criteria for comprehensive studies** that should be requested*. It has been clarified upfront in the text.
174.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.4 Fenugreek extract	SCHEER is relying on SCENIHR's "rational for inclusion" for fenugreek set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.21.1 Fenugreek). We have not changed our views in this respect and therefore recommend the following changes: The statement on p. 52, l. 23 - 24 "The complex mixtures used as additives cause tremendous harm (…) tobacco smoke" is speculative and not substantiated and we therefore recommend to delete it. We suggest to delete the following sentence on p. 52 l. 32 – 36: "The use of fruit and vegetable extract concentrates (…) could also give the impression of health protection." since Art. 7(2) and Art. 7(6) TPD are neither in SCHEER's mandate nor relevant for enhanced reporting obligations. As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 7 (9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to delete on p. 52 l.	This issue has already been addressed; please see the rational for inclusion and comments to public consultation for Opinion 1. The text was amended accordingly. The SCHEER took inspiration from the German Cancer Research Centre for its step procedure, but then developed its own proposal. See reply to comment 49.

			42 "If the evaluation shows that it is warranted to move on to step 3" We suggest deleting p. 52, l. 45 – p. 53 l. 3: "The burden of proof is on the industry to prove that the additive is safe (…) burnt form" since this statement sets new rules and standards that are not set by, and therefore does not reflect nor respect, the TPD.	The sentence has been re-phrased.
175.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.5 Fig extract	p.53 l. 15-17 Please add that experimental cigarettes containing fig extract (2000 ppm) did not exhibit increased smoke constituents levels when compared to an additive free reference cigarette (Carmines et al., & Rustermeier et al., 2002; Baker et al., 2004a,b). Tobacco smoke from test cigarettes containing fig extract at levels up to 2,000 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding fig extract. Specifically we refer to the following publications: Carmines et al., & Rustermeier et al., 2002; Baker et al., 2004a,b; Roemer et al., 2002; Baker et al., 2004c; Renne et al., 2006 Roemer et al., 2002; Gaworski et al., 1998; Vanscheeuwijck et al., 2002; Gaworski et al., 1999) p.53, l.29-31 The SCHEER's claim that "[s]everal pyrazines are also added as additives to cigarettes to impart flavour to low tar cigarettes" is speculative and should be deleted. The reference provided, Alpert, does not represent a robust and credible scientific support and should be deleted. p.53, l.31 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining	Please see answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission). The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. The text has been amended to change the word to palatability (a key component of attractiveness).

			whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. p.53, l. 35-38 Please delete line 35-38 beginning with 'The use of'. SCHEERS's referral to article 7 2a is incorrect, simply because article 7 2a does not exist in the TPD2. Nevertheless, SCHEER goes beyond its mandate as to interpret the TPD2. p.54, l.5: Please mention that the SCENIHR 2010 report commented that substances that supposedly inhibit MAO are naturally present in tobacco leaves, not added as additives. p.54, l.3-5 Please remove the claim that aldehydes "intervene directly or through the generation of new compounds in the smoke in the inhibition of MAO". This not supported by the scientific literature. p.54, l.3-7 Please delete that "[c]onverging data indicate that MAO (monoamine oxidase) inhibitors contained in tobacco and tobacco smoke act synergistically with nicotine to enhance addiction potential." No evidence is available to support this claim. Alternatively, add that this claim is speculative. Berlin and Anthenelli 2001 conceded that their conclusion regarding MAO inhibition by compounds found in tobacco smoke or tobacco can potentiate nicotine's effect is "speculation". To our knowledge, no additional information has altered this conclusion. Please refer to a more recent review (Hogg et al. 2016) that described the available data related to a role of MAO inhibition in tobacco dependence. The authors pointed out that "no data were identified to support the hypothesis that MAO inhibitors in or derived from tobacco or tobacco additives affect tobacco dependence in human smokers." p.54, l.5-7 SCHEER's coercive proposal to impose a burden of proof on manufacturers to prove that the	Thank you for pointing out the typo, it has been corrected in the text to article 7 6 a. and the text amended for clarity. Text on MAO has been amended. Text on 'burden of proof' has been amended.

			"addictiveness" properties do not exist for any particular additive is inconsistent with the TPD2. Notably, article 6(2) and Article 7(9) simply require manufacturers to provide data on the properties of the relevant additives. Please retract the "burden of proof" constraint.	
176.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.5 Fig extract	Previous studies on the pyrolysis of fig extract [5] yielded results that are slightly different from those described in the Opinion. No caramel colour, PAHs, formaldehyde, or pyrazines were produced. Instead, a complex mixture of pyrolysis products was identified. However, following additional investigations, it was concluded that none of the pyrolysis products added significantly to the levels of toxicants in smoke [2]. It is important to note that pyrolysis is likely to over-predict the thermal breakdown of non-volatile compounds, and hence smoke chemistry should also be considered as part of ingredient assessment. [61] Despite the Opinion's claim that fig extract is predominantly sugar and will therefore produce large amounts of acetaldehyde, acrolein and furfural (p.53:18ff), previous studies on the effect of sugars directly have concluded that the presence of up to 10.5% sugar in a test cigarette did not increase the biological activity of the mainstream smoke [3]. Furthermore, the addition of up to 6.2% sugar, actually reduced the mainstream yield of furfural when compared to a control cigarette [5]. Based on these findings, it is unlikely that the addition of fig extract, up to the levels used, will play a major role in the toxicity of tobacco products, despite the presence of sugar per se. During cigarette combustion, groups of tobacco ingredients, including fig extract at 1.17 %, generally had no effect on or reduced the levels of	Please see answers to comment 174.

			most of the measured smoke constituents, and levels of none were increased. Furthermore, these changes did not affect the smoke's in vitro cytotoxicity, in vitro bacterial mutagenicity, in vitro mammalian genotoxicity, or inhalation toxicity [5]. These results are consistent with other extensive data sets available in the public domain, and ascertain the fact that the additives should be studied in comparative test cigarettes in accordance with the fact that their contributions to the smoke components are offset by the reduction in tobacco contributions. The Opinion states that "the burden of proof is on the industry to use the proposed step-wise system (…) to prove that the additive is safe on all counts of toxicity, addictiveness and characterizing flavour in the unburnt and burnt form" [p.54:5-7]. This is beyond the scope of both Article 6 TPD2 and the Terms of Reference and we are unaware of any such requirement under the TPD. SCHEER states that fig extract "can thus give an impression of providing a health benefit to the consumer, so could be considered under the TPD Article 7 2 a." Considerations on matters relating to Article 7 are beyond the scope of the Terms of Reference.	
177.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.5 Fig extract	Page 53, Lines 15-17: SCHEER should be made aware that there are various studies in the public literature which assess the behaviour of fig extract in a combusted cigarette and its biological effects (Baker et al., (2004), Carmines et al., (2002) and Renne et al., (2006) at levels several multitudes and in some cases magnitudes higher than those used for commercial cigarettes. Even under these	Please see the answers to comment 1 for a comprehensive explanation about the SCHEER reasoning on CT and comment 26 (studies for submission). The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the

			exaggerated inclusions, no significant differences between control and test cigarettes were observed in any of these studies. Page 53, Lines 35-38: No communications to this effect are made to our consumers. Additives may be added to tobacco products during manufacture. Additives (for example, flavourings typically used in food) are used in very small quantities in some brands to enhance their overall flavour characteristics and aroma, giving brand variants their own distinctive style, in line with consumer preferences. Additionally, due to the known health risks of smoking, we do not claim that tobacco products are "safe", neither do we make claims that any Tobacco Product is "safer" than another (unless endorsed and/or required by regulatory authorities). Page 53, Lines 39-43: These are all constituents naturally found in cigarette smoke. SCHEER should note that the addition of fig extract (CAS 90028-74-3) at 11,700 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes (Baker et al., 2004). Page 54, Lines 1-3: It would benefit the reader to provide an appropriate reference or to delete this point if it cannot be substantiated. In this Preliminary Opinion SCHEER outline several hypotheses, not validated by scientific evidence, and contradicting available research (Mueller et al.	assessors will evaluate them on the basis of a WoE approach, considering their relative relevance, in view of the SCHEER indication about CT. This is a general statement about the general population perception. The SCHEER was not accusing any company of explicitly communicating this type of message. For CT, please see the answer to comment n°1. The available studies, based on robust methods and credible scientific research, will be collected in Step 1.

			2000). We support evidence based on robust methods and credible scientific research, on which valid assessment can be based.	
178.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.5 Fig extract	PMI does not use fig extract and will not carry out enhanced testing of the additive. SCHEER is relying on SCENIHR's "rational for inclusion" for fig extract set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.21.2 fig extract). We have not changed our views in this respect and therefore recommend the following changes: The statement on p. 53, l. 29 - 31 "The complex mixtures (…) tobacco smoke." is speculative and not substantiated and therefore we suggest to delete it. We suggest to delete p. 54 l. 35 – 38: "The use of fruit and vegetable extract concentrates (…) could be considered under the TPD Article 7 2 a." Art. 7(2) and Art. 7(6) are neither in SCHEER's mandate nor relevant for enhanced reporting obligations: We suggest to delete p. 54, l. 5 - 7: "The burden of proof is on the industry . . ." since this statement sets new rules rather than reflect and respect the rules set by the TPD.	If PMI does not use any or all additives on the priority additives, the responsible regulators should be informed accordingly to avoid the enhanced testing of those additive/s. See answers to comment 174 and 175.
179.	Henkler, Frank, German Federal Institute for Risk Assessment	2.5.6 Geraniol	The BfR suggests to amend section 2.5.6 on geraniol (page 54-55) in order to refer to its innate property to activate cold-menthol "transient receptor potential melastatin 8" (TRPM8). TRPM8 mediates a pleasant cooling sensation in the upper airways that can mask the harsh and irritation effects of tobacco smoke. TRPM8 activation is	Thank you for the comment. The information and the reference have been added to the Opinion.

	(BfR), frank.henkler@bfr.bund.de, Germany		therefore a suitable physiological mechanism to promote inhalation, especially by unexperienced smokers during the initiation and adoption stages. Geraniol was identified and confirmed as TRPM8 agonist by Behrendt et al. Br J Pharmacol 2004;141:737-745 and Lübbert et al. PloS One 2013;8:e77998. This important information should be included into the SCHEER report.	
180.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.6 Geraniol	p. 54, l. 24-26 Please note that tobacco smoke from test cigarettes containing geraniol at levels up to 3.5 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding geraniol. (Carmines et al., & Rustemeier et al., 2002; Baker et al., 2004a; Roemer et al., 2002; Baker et al., 2004c; Renne et al., 2006; Vanscheeuwijck et al., 2002) p.54, l.32-36 Please note that EU guidance documentation states 'it is clear that contact sensitization is systemic in nature and that there is no reason to suppose that encounter of sensitized animals with the relevant contact allergen at respiratory epithelial surfaces will not cause an adverse immunologic reaction. However, it is important to note that in reality only a very few precedents for the elicitation of pulmonary reactions by skin sensitizing chemicals in humans have been observed, and in practice it may not represent a significant health issue. (Chapter R.7a: Endpoint specific guidance Version 4.1 – October 2015.) Please note that there is currently a Geraniol General Population inhalation DNEL (Derived No Effect Level) of 47.8 mg/m³ (ECHA REACH registration dossier updated 18th March 2016) p.55, l.20 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article	Please see the answer to comment n°1 for the SCHEER position on CT. The exposure levels are however very important to allow a risk assessment based on the hazard characterisation of the additive. The SCHEER agrees that sensitisation is a systemic reaction. There is no disagreement between the SCHEER and the commenter. The SCHEER welcome the existence of such data that will help TI to fulfil the task in the 18- month timeframe. The information has been added to the Opinion. The sentence has been re-worded.

			6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. p.55, l. 22-23 Please remove the sentence "one of the factors potentially contributing to attractiveness" as this term is inconsistent with the TPD2. According to Article 7 (1), "'characterising flavour' means a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product". p.55, l.20 It is crucial that the concept of "addictiveness" is adequately defined and that "addictiveness" is objectively measureable before it may be considered as a basis for regulation. 6 years have passed by since the release of the 2010 SCENIHR report, which concluded: "At present it is not possible to evaluate whether additives increase the addictive potency of the final tobacco product." To our knowledge, no additional information has altered this conclusion. A scientifically valid approach to evaluating the dependence potential of a given additive is not available up to now.	The comment was accepted and the sentence has been deleted. The definition of addictiveness has been included in the revised version, although it was already clearly defined in the Opinion I, in line with the SCHENIHR 2010 document.
181.	Ureel, Ludwig, British American Tobacco,	2.5.6 Geraniol	Assuming 100% transfer to mainstream smoke, an extreme consumption of 40 cigarettes/day, and the maximum application level of 23ppm used by BAT, the total maximum exposure/day for a 70kg	The SCHEER welcomes the existence of such data/evaluation that will help TI to fulfil the task in the 18 months.

	ludwig_ureel@bat.com, United Kingdom		smoker, as a worst case scenario, would be less than 0.01mg/kg body weight/day. This demonstrates that possible exposure from cigarettes is substantially less than the level causing adverse effects in the animal toxicity studies reported in the Opinion [p.54:20-23]. Furthermore, neither the Food and Agriculture Organization and World Health Organization Joint Expert Committee on Food Additives (JECFA) [25], or the International Agency for Research on Cancer (IARC) [26] have highlighted any evidence which indicates that food grade geraniol contains methyl eugenol. The statement in the Opinion that "[n]o levels that could be considered safe for the majority of consumers could be established from the available data." (p.54:19-29) is a misrepresentation of what was quoted in the original source [21]. The Scientific Committee on Consumer Safety actually states "[a]s data from human dose elicitation experiments are very limited in several respects, no levels that could be considered safe for the majority of contact allergic consumers could be established for individual substances." Whilst geraniol is recognised as a skin sensitiser, albeit in much higher levels than occur in cigarette smoke, contrary to the assertions in the Opinion there is no data to suggest it is a respiratory sensitiser, or is even likely to be one (see both its GHS classification [22] and CLP classification [23]). Furthermore the European Chemicals Agency (ECHA) states "[t]here is a known link between skin and respiratory sensitisation. Most if not all known respiratory sensitisers are also skin sensitisers, while the converse is not necessarily true" [24].	 Again, this will make easier to respond to the request. The text was copied from Opinion 1. Please consider that CLP classification on ECHA web site clearly indicate that for the endpoint regarding potential for respiratory sensitization it is not classified due to 'data lacking'). Therefore the absence of classification does not mean the substance does not have those properties. The SCHEER agrees that skin sensitisers are not necessarily respiratory sensitisers, but this will be evaluated on the basis of the WoE approach by the assessors, once all the info collected by TI has been provided.

			Demonstration of respiratory sensitisation is highly complex, and SCHEER has not provided any validated in vitro models to study it. The summary report from the Sens-it-iv end Congress, Brussels, November 2011 [27] concluded "In vitro assessment of respiratory sensitizers has not yet reached the same level as in vitro assessment of skin sensitizers. The main reason for this is the cellular (about 60 different cell types) and structural complexity of the respiratory tract, stretching from the nose down to the alveolar space in the lungs. In addition, the lack of a qualified human data set, as well as of a trustworthy in vivo animal model, makes it difficult to establish a set of compounds useful for test development and evaluation."	SCHEER agrees. Other kind of info (e.g. non testing methods) or information already available on animal models could be used to allow an evaluation based on a WoE approach.
182.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.6 Geraniol	Page 54, Lines 15-23: SCHEER highlighted the possible sensitisation effects of geraniol, "no levels are considered safe for the majority of users". When IFRA calculated the NESIL (no effect sensitisation induction level), the calculated value was 11.8 mg/cm2, with the potency based on animal data, classified as weak (IFRA). There are no reports of geraniol being a respiratory sensitiser in humans. There are also no validated tests for respiratory sensitisers. At typical reported use levels in tobacco products (10ppm Baker et al., 2004) the levels are too low to induce dermal sensitisation. Geraniol has been reported to attenuate important features of allergic asthma in mice possibly through modulation of TH1/TH2 balance and the activation of NFR2 antioxidant response (Xue Z et al., 2016). Geraniol is not added for any health effects and has been used as a flavour additive for many years.	Doing a full risk assessment of geraniol and the other additives on the list is not a task for the SCHEER (see the ToR). Once all the info collected by TI according to the step procedure has been provided, it will be evaluated on the basis of the WoE approach by the assessors at MS level.

183.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.6 Geraniol	SCHEER is relying on SCENIHR's "rational for inclusion" for geraniol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.13 Geraniol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete "(one of the factors potentially contributing to attractiveness)" on p. 54, l. 12 and on p. 55, l. 22 – 23. We also suggest to delete the term "attractiveness" on p. 55, l. 20. As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 6(2), (3) and Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to delete p. 54, l. 41 – p. 55, l. 1 - 4 "In case of positive results, the use of geraniol as a tobacco additive should be not allowed and no additional testing would be necessary. In case it could be demonstrated that geraniol is not a respiratory irritant and sensitizer, the additive can enter the procedure for evaluation."	The comment has been accepted and the text has been changed accordingly. The SCHEER used the DKFZ approach as a starting point and then developed its own step wise procedure. If the reference is to the approach of not endorsing CT, please see answer n°1 to comment n°1. The SCHEER considered that whenever the available data coming from step 1 and 2 are robust enough to carry out any WoE based evaluation, a decision can be taken without needing further testing to resolve uncertainties. To explain it in greater detail, the texts in the general procedure and in the specific paragraph have been amended.
184.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202	2.5.7 Glycerol	p.55, l.34-36 Please note the following: A Glycerol General Population inhalation DNEL (Derived No Effect Level) of 33 mg/m³ exists for the most sensitive endpoint: irritation (respiratory tract). p.55, l.38-42, P. 56, l.9-15 Please note that to assess the effect of added glycerol to cigarettes,	Noted. The information presented in the paragraph cited is from Opinion 1. Additional information such as the DNEL of 33 mg/m3 referred to in this comment is useful when assessing the risks from inhalation.

	Geneva, Switzerland, Javier.Martinez@jti.com, Other		comparative studies are currently best practice to discriminate between the formation of acrolein from tobacco and the potential additive effect of glycerol when used as additive. Please consider that pyrolysis does not provide a robust prediction of the compounds that might be formed from additives during cigarette smoking. Please note that the generation of acrolein through degradation of glycerol in the tobacco blend has been studied quantitatively in a burning cigarette (Yip et al., 2010). Less than 0.08 % of the blend glycerol were converted to acrolein in mainstream smoke for all cigarette designs and smoking regimes tested. Together these studies demonstrate that glycerol is not a principal source for acrolein formation. The net effect is a general reduction in smoke yields as reported for nicotine, nitrogen-containing smoke constituents, aldehydes, phenols and others (Rustemeier et al., 2002). Adding glycerol at the 5 % level to tobacco did not increase acrolein in mainstream smoke (Carmines&Gaworski, 2005). The addition of Glycerol reduces the tobacco weight in the finished product and consequently the amount of combustible precursors for the generation of smoke constituents including those generating acrolein (McAdam et al., 2011). In conclusion, the sentence on page 56, line 9 to 11 should be removed. Pyrolysis has been developed as a screening tool to provide a qualitative (and at best a semi-quantitative) fingerprint of the test material. In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative	The SCHEER agrees that glycerol is not a principal source for acrolein formation and that small (<0.1%) of the blend is converted to acrolein. This is now reflected in the text included under 'priority areas'. See previous comments regarding pyrolysis (e.g. n°72). Noted. This paragraph has been modified to take into account this comment.

			measurement. p.56, l. 3-7 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Only taste and smell are considered in the definition for characterizing flavor provided by the TPD2. According to Article 7 (1), "'characterising flavour' means a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product". Consequently, the reference regarding "attractiveness" is irrelevant and should be removed. Please remove this paragraph. p.56, l.16-17 Please note that contrary to SCHEER's statement, extensive assessments on the systemic effects of glycerol are available. (see, e.g., CIR (2015). Safety assessment of glycerin as used in cosmetics. Final report. January 14, 2015.	Please see the previous replies on attractiveness. The SCHEER welcomes the fact that TI already has a number of studies ready for submission. They should be presented together with all the available studies (Step 1 and 2) and then the assessors will evaluate them on the basis of a WoE approach, considering their relative relevance.
185.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.7 Glycerol	The opening statement: "Glycerol is added as a humectant to tobacco (to help keep it moist)" is at odds with the statement in the introduction (2.1) "it should be noted that …additives in tobacco products have no health or other benefits to the consumer." The benefit of keeping tobacco moist is essential to the pliability and malleability of fine-cut tobacco which allows consumers to roll their own cigarettes. Pyrolysis studies conducted under conditions which simulated those of a burning cigarette [4] demonstrated that 99.5% of the glycerol would be	See previous comments on this issue. Section 3.1 has been amended to address this. This is the rationale for inclusion taken from the previous Opinion. so this has not been changed in the text. The fact that acrolein can be generated from the combustion of tobacco has already

			transferred into the mainstream smoke intact. Two minor pyrolytic breakdown products were identified but despite the claim in the Opinion neither were acrolein. It is important to note that acrolein is generated from combustion of tobacco and other biopolymer components of a cigarette and not glycerol per se. The Opinion asserts (p.56:12-13) that "the relationship between added glycerol and acrolein is unclear" – this is at odds with the assertion that "less than 0.1% of the blend glycerol is converted to acrolein in mainstream smoke" (p.38:55). On the basis that such a large proportion of glycerol remains intact in mainstream smoke, it is questionable that the tobacco industry should have to provide extensive reporting despite its natural occurrence in the body, its use as an intermediate in many industrial applications, and its presence in consumer products such as pharmaceuticals, cosmetics, tobacco, food and drinks as well as numerous other products such as paints, resins and paper [29]. These industries are not required to provide equivalent data. Extensive studies published by the Tobacco Industry have also shown that the use of glycerol as a tobacco ingredient at typical application does not increase the toxicity of cigarette smoke. We note SCHEER's comments regarding the possible systemic effects of glycerol, and welcome this opportunity to draw their attention to a previously published OECD SIDS Assessment Report for this additive [29]. This report identifies that there is a potential for exposure through a number of different routes, occupationally via inhalation and skin	been acknowledged in step 2 (priority areas). Paragraph has been amended to reflect this. Any additional information available should be included in the full risk assessment. Once all the information collected by TI according to the step procedures outlined in the Opinion is provided, it will be evaluated by the assessors at MS level.

			contact, whilst consumers may be exposed both orally and dermally. The report concludes that "[g]lycerol is absorbed following ingestion and metabolised by glycerokinase in the liver to carbon dioxide and water or incorporated in the standard metabolic pathways to form glucose and glycogen. The weight of evidence indicates that glycerol is of low toxicity when ingested, inhaled or in contact with the skin." The report goes on identify that following the inhalation of glycerol aerosol, a No Observed Adverse Effect Concentration (NOAEC) of 662 mg/m3 was determined for systemic effects. As such, the only reason for glycerol's inclusion in the Opinion is its alleged effect on attractiveness (p.56:3), which is not among the outcomes that the studies are meant to assess (Article 6.2(a)-(d)). Glycerol, as the Opinion notes, is predominantly transferred to smoke unchanged, and as it is added to tobacco at relatively high levels of 1-5% it is likely to have a diluent effect on tobacco smoke rather than an enhancing one. Glycerol is also a principal component of e-cigarette vapour and as such was extensively reviewed in the Royal College of Physicians report [74].	Noted. This information should be presented together with all the available studies (Step 1 and 2) and then the MS assessors will evaluate them on the basis of a WoE approach, considering their relative relevance. Noted, sentence has been changed to remove the reference to attractiveness. e-cigarettes are not included in this Opinion, but if considered relevant this information could be presented (steps 1 and 2), together with information on any other relevant studies.
186.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.7 Glycerol	Page 55, Lines 37-42 & Page 56, Lines 9-13: Purkis et al. (2011) states that pyrolysis studies on glycerol indicate 100% intact transfer of the compound into mainstream smoke. Additionally, Yip et al. (2010) have shown that less than 0.1% of glycerol is converted into acrolein for all cigarette designs when using either the ISO or Canadian machine smoking regimes. Two techniques have	This is acknowledged in the document.

			shown that Glycerol transfers virtually intact and is not a significant source of acrolein. A notable example is glycerol, investigated by Roemer et al (2010). Even when glycerol was added to cigarettes at significant quantities (0, 1.5, 3.3, 5.5% by weight), none of the compounds predicted by pyrolysis, such as acrolein, could be detected at higher levels in the smoke under ISO Page 56, Lines 14-15: The behaviour of glycerol in a cigarette with a complex mixture of additives has already been investigated by Baker et al., (2004), Carmines et al., (2002) and Heck et al., (2002). Glycerol was not observed to significantly change the biological activity of the smoke in these studies. Page 56, Lines 16-17: Glycerol occurs endogenously in the body and has been approved for use as a food additive by both JECFA and the SCF. Both of these do not specify a set acceptable daily intake. This additive has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints). The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/. We request that SCHEER provides a list of validated in silico / vitro assays which can thoroughly assess the systemic effects of glycerol.	See above. This information should be presented together with all other available studies (Step 1 and 2) and then the MS assessors will evaluate them on the basis of a WoE approach, considering their relative relevance. It is outside the ToR of this Opinion to look at the REACH dossier. Since data are available, they will be collected in Step 1, limiting the need for further testing. See the previous answer in other parts of the Opinion.

187.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.7 Glycerol	SCHEER is relying on SCENIHR's "rational for inclusion" for glycerol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.14 Glycerol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete the term "attractiveness" on p. 56 l. 3 – 6. We suggest the amended text be "Humectants are added to trap water, thereby keeping the moisture in the tobacco and preventing it from drying out. Glycerol is, therefore, considered to positively influence cigarette smoking, given that humidification improves the palatability of cigarettes."	The text has been changed to take on board this comment.
188.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.8 Guaiacol	p.56, l.23 Please remove the sentence "one of the factors potentially contributing to attractiveness." This is inconsistent with the TPD2. According to Article 7 (1), "'characterising flavour' means a clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herbs, alcohol, candy, menthol or vanilla, which is noticeable before or during the consumption of the tobacco product". p.56, l. 24-25 and p.57, l.14-15 Not a single study provides any evidence that Guaiacol "use as a local anesthetic can enhance smoke inhalation, thus potentially contributing to addictiveness." This is pure speculation and should be deleted. p. 56, l. 29-35 Please note that Guaiacol has been	The word attractiveness has been deleted. The text has been changed to take on board this comment This is the rationale for inclusion taken from the previous Opinion. Although there is no specific evidence that guaiacol can contribute to addictiveness, the fact that it could be used as a local anaesthetic (one of the mode of action contributing to addictiveness) makes it possible to hypothesise. The burden of proof is on TI. The availability of these studies will simplify the work of TI in

			documented as non-mutagenic when tested in vivo (ECHA REACH registration dossier updated 27th December 2015). Guaiacol was tested as part of an additive mixture in cigarettes in comparison to an additive free reference cigarettes as part of a 90-day nose-only smoke inhalation study. The results showed no significant increase in the severity or incidence of respiratory tract findings where histopathological and histomorphometric assessments had been conducted. (Baker et al., 2004c). Tobacco smoke from test cigarettes containing guaiacol at levels up to 12 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding guaiacol. Specifically we refer to the following publications: Baker et al., 2004a; Baker et al., 2004c; Gaworski et al., 1998; Gaworski et al., 1999.	providing the requested information. For CT, please see the answer to comment n°1.
189.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.8 Guaiacol	We note the comments in the Opinion regarding the possible mutagenicity of guaiacol [p.56:32-34]. However, we would like to highlight to the Committee the existence of an in vivo genotoxicity assay carried out to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test) in both male and female mice. This concluded that "under the experimental conditions reported, the test item did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse. Therefore, Guaiacol is considered to be non-mutagenic in this micronucleus assay". The findings are included in the REACH registration dossier for guaiacol [35]. This in vivo assay would be considered superior to and negates the results of the in vitro SCE assay cited in the Opinion. Accordingly, we consider that the genotoxic	The availability of these studies will simplify the work of TI in providing the requested information. SCHEER welcome the presence of an OECD Guideline 474-compliant study demonstrating that guaiacol is not genotoxic. Since the SCHEER could not analyse the study, it cannot conclude on it. However, its positive evaluation will allow guaiacol to enter the step procedure, not being excluded upfront, due to CMR properties in the unburnt form (see art. 7).

			potential of guaiacol is no longer under question. Furthermore, the highest level tested, 500 mg/kg bw is over 90,000 times the possible worst case exposure to guaiacol from cigarettes. Further studies showed that a mixture of tobacco additives, including guaiacol applied to tobacco at 12ppm generally had no effect on, or reduced the levels of most of the measured smoke constituents, although some increase in the level of styrene was observed [1] [2] [3] . However, no impact on the smoke's in vitro cytotoxicity, in vitro bacterial mutagenicity, in vitro mammalian genotoxicity, or inhalation toxicity was observed. These results are consistent with those other extensive data sets available in the public domain. As part of our risk assessment, if we assume 100% transfer to mainstream smoke, an extreme consumption of 40 cigarettes/day, and the maximum application level of 12ppm used by BAT, the total maximum exposure/day for a 70kg smoker, as a worst case, would be less than 0.01mg/kg body weight/day. We draw SCHEER's attention to the large amount of published literature regarding the testing of tobacco additives, under conditions of use. Pyrolysis studies conducted under conditions which simulated those of a burning cigarette [4] demonstrated that over 92% of guaiacol would be transferred into the mainstream smoke intact. Small amounts of other pyrolytic breakdown products were identified, but the authors concluded that none of these would add to the levels of toxicants in cigarette tobacco smoke. In fact, it was estimated that the total amount of these would equate to just over 0.2µg/cigarette based on typical application level of	The availability of these studies will simplify the work of TI in providing the requested information. However, please note that doing a full risk assessment of guaiacol and the other additives on the list is not a task for the SCHEER (see the ToR). Once all the info collected by TI according to the step procedure has been provided, it will be evaluated on the basis of the WoE approach by the assessors at MS level.

			the parent compound.	
190.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.8 Guaiacol	SCHEER is relying on SCENIHR's "rational for inclusion" for guaiacol set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.15 Guaiacol). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete "(one of the factors potentially contributing to attractiveness)" on p. 56, l. 22. As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 6(2), (3) and Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to delete: p. 57, l. 10 - 11 "In case there are no objections, the evaluation should proceed to step 3." p. 57, l. 15 - 16 "In case there are no objections, all the other toxicity end-points should be considered."	 The suggestion has been accepted and the text has been changed accordingly. The SCHEER used DKFZ approach as a starting point, but developed its own step wise procedure. If the reference is to the approach of not endorsing CT, please see answer n°1 to comment n°1. The text has been modified for greater clarity.
191.	Vizée, Huub, delfortgroup, huub.vizee@delfortgroup.com, Austria	2.5.9 Guar gum	2.5.9 Guar gum Synonyms: Guaran, Guar Flour, Jaguar - CAS number: 9000-30-0 (Guar depolymerised CAS number: 68411-94-9) and others. Guar Gum is a natural substance and used in the papers which wrap the tobacco. Guar Gum in itself has no CRM properties in unburnt form and only	Please see the answers to comment n°1 for a comprehensive explanation about the SCHEER's reasoning on Comparative Testing.

			formed combustion products could, according to SCHEER, possibly be harmful. However; SCHEER claims a percentage usage that doesn't reflect the reality. In paper the percentage of Guar Gum is much lower and its contribution to the overall toxicity of the combustion of a tobacco product is not significant. Looking at Guar Gum as a single individual additive and carrying out pyrolysis on this additive will not deliver any substantial information. As stated by the Commission SCHEER should look at "studies that take into account the intended use of the products concerned and examine in particular the emissions resulting from the combustion process involving the additive concerned. The studies shall also examine the interaction of that additive with other ingredients contained in the products concerned." In other words, comparative studies should be carried out and not only pyrolysis on a single individual additive. Because of the low percentage of Guar Gum in a tobacco product it is to be expected that Guar Gum will not increase the addictiveness, toxicity or the CMR properties of the tobacco product to a significant or measureable degree. Also in Article 7, Regulation of Ingredients, clause 1 from the Tobacco Product Directive it is stated: "Member States shall not prohibit the use of additives which are essential for the manufacture of tobacco products, for example sugar to replace sugar that is lost during the curing process, provided those additives do not result in a product with a characterising flavour and do not increase to a significant or measureable degree the addictiveness, toxicity or the CMR properties of the tobacco product." As Guar Gum is essential for the manufacture of tobacco products, in this case paper, and it does not result in a product with a characterising flavour,	The SCHEER disagrees with the comment.

			because of the low percentage in the final tobacco product, and it does not increase to a significant or measureable degree the addictiveness, toxicity or the CMR properties of the tobacco product, which can be concluded when comparative studies would be carried out, Guar Gum should be taken from the list of 15 additives.	
192.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	2.5.9 Guar gum	p.57, l. 30-34 Please add that Baker & Bishop 2005 reported the results from a guar gum pyrolysis study. Studies in which smoke chemistry data from test cigarettes including guar gum as an additive at 22,410 ppm (Coggins et al., 2011b) and at 100 ppm (Baker et al., 2004a,b), were compared to cigarettes where guar gum, were not included by SCHEER. The results showed that there was no statistically significant increases in levels of "Hoffmann analytes" in the smoke. Please consider that pyrolysis does not provide a robust prediction of the compounds that might be formed from additives during cigarette smoking. p.57, l.37-40, p.58, l.1-2, p.58, l.22-24 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Therefore, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". Consequently, the reference to "attractiveness" is irrelevant and should be removed. p.58, l. 6-9 Please note that Baker & Bishop 2005 reported the results from a guar gum pyrolysis study. Studies in which smoke chemistry data from test cigarettes including guar gum as an additive at 22,410 ppm (Coggins et al., 2011b)	Please see the answers to comment n°1 for a comprehensive explanation about the SCHEER's reasoning on Comparative Testing. The word attractiveness has been deleted. Text has been changed to take this comment on board. Please see the answers to comment n°1 for a comprehensive explanation about the SCHEER's reasoning on Comparative Testing.

			and at 100 ppm (Baker et al., 2004 a,b), were compared to cigarettes where guar gum, were not included by SCHEER. The results showed that there were no statistically significant increases in levels of "Hoffmann analytes" in the smoke. This approach is consistent with the TPD2 requirement, Article 6(2) (a), (d) and Article 7(9), to test under the condition of use. Several toxicological studies have been used to assess mixtures of additives applied to experimental cigarettes (Carmines et al., 2002; Baker et al., 2004a-c; Renne et al., 2006), while others have focused on single additives (Heck et al., 2002; Lemus et al., 2007; Stavanja et al., 2008; Coggins et al., 2011a-i; Gaworski et al., 2011). The assays used have been originally developed for the regulatory assessment of industrial chemicals or pharmaceutical compounds. Collectively, the assays evaluate cytotoxic/chronic irritative, mutagenic and carcinogenic potential of tobacco products. Tobacco smoke from test cigarettes containing guar gum at levels up to 22,410 ppm and additive free reference cigarettes were tested in a battery of in vitro and/or in vivo test(s). In these studies, the biological activity of the smoke was not altered by adding guar gum (Baker et al., 2004a; Coggins et al., 20011b; Gaworski et al., 2011; Baker et al., 2004c). In light of the lack of internationally standardized pyrolysis methods and pyrolysis models, and taking into account, that different models will provide different output, quantitation at this stage might be a misleading approach. As a result, it does not provide data that can be directly correlated with cigarette smoke. Consequently, pyrolysis should not be used for a quantitative measurement. p.58, l.16 The guidance provided by SCHEER goes	All cited studies were comparative studies, therefore please see our comments on limitation of comparative testing and pyrolysis (comment n°1).

			beyond requirements as defined in of TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, "addictiveness" and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Therefore, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, "addictiveness" or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation.	Please see the answer given for the same issue in the general text of the Opinion.
193.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	2.5.9 Guar gum	All guar gum used by BAT is food grade, and so meets the purity requirements of E412, as defined in COMMISSION REGULATION (EU) No 231/2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council. This is to ensure that levels of residual solvent and heavy metal contamination are minimised, whilst the necessary microbiological criteria are met. Pyrolysis studies conducted under conditions which simulated those of a burning cigarette [5] demonstrated that whilst guar gum largely broke down, constituents such as furfural, cresol and benzene would only equate to about 0.15µg/cigarette based on typical application level of the parent compound. Whilst guar gum does contain polysaccharides, the evidence does not support the suggestion in the Opinion that on combustion formaldehyde is generated [p.57:30-34], and transfers into the mainstream smoke. As guar gum is a complex	If the information is available, it will be presented as relevant with information retrieved in Step 1. Please see the general answer on pyrolysis (e.g. n° 72). All cited studies were comparative studies, therefore please see our comments on limitation of comparative testing and pyrolysis (comment n°1).

			natural material it is logical to test it as such, to take account of interactions between compounds and possible additive effects. Studies established that during cigarette combustion, the presence of tobacco additives, including guar gum, at a typical application level of 100ppm either reduced, or had no effect on the levels of the measured smoke constituents [1] [2] [3]. The studies also demonstrated no changes were observed in the in vitro or in vivo biological activity of the mainstream tobacco smoke. The findings of these studies are consistent with other extensive data sets also available in the public domain.	
194.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	2.5.9 Guar gum	Page 58, Lines 3-4: This statement appears to be derived from a material safety datasheet and is not applicable at the levels Guar gum is added to a cigarette. Page 58, Lines 13-16: No validated studies exist for the determination of pyrolysis products from tobacco additives. Moreover, pyrolysis studies are not representative under the conditions required for the intended use, whereby additives are combusted with tobacco, as required under Art. 6.3 of the Directive. SCHEER will be interested to note that a pyrolysis study has already been performed. Baker and Bishop (2005), observed that Guar gum broke down. All pyrolysis constituents formed are naturally found in cigarette smoke and pyrolysis of Guar gum would give rise to negligible quantities of these compounds compared to typical levels already present in tobacco smoke. SCHEER should note that Coggins et al., (2011) assessed the smoke chemistry of cigarettes with	The SCHEER disagrees. Please see the answers to comment n°1 for a comprehensive explanation about the SCHEER reasoning on Comparative Testing. All cited studies were comparative studies, therefore please see our comments on limitation of comparative testing (comment 1).

			added Guar gum with a target inclusion level of 22,410 ppm. Compared to a control cigarette with no test additive there were no statistically significant changes in smoke chemistry. Additionally, the biological activity (assessing in vitro genotoxicity and in vivo toxicity) of the cigarette smoke with Guar gum was no different than the control cigarette. Baker et al., (2004) observed no statistically significant changes in smoke chemistry between cigarettes with 100ppm Guar gum added or control cigarettes.	Please see the answer to comment related to pyrolysis studies.
195.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	2.5.9 Guar gum	SCHEER is relying on SCENIHR's "rational for inclusion" for guar gum set forth in opinion 1. We disagree with parts of this rational and have commented accordingly in our September 2, 2015, comments on "SCENIHR Preliminary opinion on Additives used in tobacco products (Opinion 1)", comment to 3.3.16 Guar gum). We have not changed our views in this respect and therefore recommend the following changes: Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete "and contribute to the attractiveness of smoking" on p. 57, l. 39. As discussed in our comment to the Abstract, the DKFZ approach is not consistent with Art. 6(2), (3) and Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. We therefore suggest to amend p. 58, l. 17 - 22 as follows:	Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour". See the answer to same comment in the abstract. Agreed. Text in the Opinion has been modified.

			"In case of positive results for genotoxicity/carcinogenicity of its pyrolysis products additional testing would be required for a Weight of Evidence assessment. Step 3: The assessment of its pyrolysis products on . . ."	
196.	No agreement to disclose personal data	2.5.9 Guar gum	Guar gum is used in the cigarette paper production to improve its formation (and as a consequence to reduce the variability of air permeability, which is the primary factor to control cigarette deliveries) and to increase its mechanical properties. The maximum amount is 1,5% based on cigarette paper weight (and less than 0,1% based on cigarette weight). It is clear from a scientific point of view that the substances and its amount formed during the pyrolysis of an additive alone could not be the same as the ones formed during the pyrolysis of the additive as part of a product, in this case a cigarette. Even the most sophisticated pyrolysis conditions are not able to reproduce the conditions during the smoking of a cigarette. As mentioned in the Preliminary Opinion II on Tobacco Additives, the studies carried out by the tobacco industry based on pyrolysis on a comparative basis where a research cigarette is machine smoked with and without the additive present ("The pyrolysis of non-volatile tobacco ingredients using a system that simulates cigarette combustion conditions ",Richard R. Baker and Louise J. Bishop, J. Anal. Appl. Pyrolysis 74 (2005) 145–170) do not show a significant impact of the different additives studied, among them cellulose and guar gum.	Please see the answers to comment n°1 for a comprehensive explanation about the SCHEER reasoning on Comparative Testing and pyrolysis.

			In the case of guar gum and in relation to its behaviour as a component of cigarette paper, with a maximum amount of 1,5%, in our opinion the most logical way to analyze its effect on the formation of toxic pyrolyzates is to analyze the whole paper. First, because it is expected to have similar compounds to cellulose after pyrolysis (1) and, when producing the paper, the guar gum substitutes the same amount of cellulose because the grammage of the paper is constant. And, second, because in a cigarette the paper burns as a whole. If the decision is to analyze the additive alone, considering the complexity of the composition of the cigarette smoke, an intermediate way is to see if there is an increase of the compounds detected in the pyrolysis of the additive alone in the products formed by smoking a cigarette prepared with paper without additive with the same analysis performed in a cigarette prepared with paper with the maximum amount of additive. (1): "The pyrolysis of non-volatile tobacco ingredients using a system that simulates cigarette combustion conditions ",Richard R. Baker and Louise J. Bishop, J. Anal. Appl. Pyrolysis 74 (2005) 145–170 Regarding attractiveness, Scientific Committee on Emerging and Newly Identified Health Risks, SCENIHR) has concluded that there are no validated methods or reliable data for measuring or assessing the "attractiveness" of ingredients in tobacco products (Addictiveness and Attractiveness of Tobacco Additives (ISBN 978-92-79-12788-5), 2010, S.91).	

			The increase of the product addictiviness by the addition of guar gum is based on the theoretical production of acetaldehyde. The SCENIHR issued a report concluding that acetaldehyde is metabolised very quickly in the body and that no mechanism could be found by which sugars contribute to increased dependence (SCENIHR : Addictiveness and Attractiveness of Tobacco Additives (ISBN 978-92-79-12788-5), 2010, S.45). Finally, and as stated at the beginning, the use of guar gum is for paper production purposes, to enhance and assure the uniformity of the properties of the paper, as it reduces the variability of some important properties such as air permeability. By no means is for increasing attractiveness and/or addictiveness.	Please see the answers above to the addictiveness issue.
197.	Steinlin, Heinrich, Polygal GmbH, Turmstr. 4, D-78467 Konstanz, h.steinlin@polygal.ch, Germany	2.5.9 Guar gum	SEE Attachment  2016.09.20_Polygal_ Comments_to_SCHEE	Thank you for the comment and valuable additional information.
198.	Colombo, Maurizio, Biologist, famanina@libero.it, Italy	2.5.9 Guar gum	The text of Preliminary Opinion about the additives used in tobacco products, prepared by SCHEER and the related literature, with a number of comments about the inclusion of Guar Gum in the list of concern chemicals, was analyzed Apart the use in cigarette paper, the use of guar gum as additive is mainly in tobacco as binder is limited and at where the typical concentration - cited in the text – is 0.6-1.8% is related to minimal	Thank you for the comment and valuable additional information.

			part of the reconstituted tobacco where other additives are mainly used. Some CMR substances are indicated as pyrolysis by-products of guar gum, but aromatics like benzene or benzo(a)pyrene cannot be generated by polysaccharide structure as such. The studies reports some evidences about aromatics generated during the test, but there is no a clear picture of the purity of guar gum used. Guar Gum is produced in tropical countries and only the food grade Guar Gum is controlled for the presence of contaminants or pesticide residuals. In addition no information are indicated about the analytical methodology used and the related limit of detection, or (LOD) or limit of quantification (LOQ). Guar Gum is Galactomannan, a polysaccharides of a mannose backbone with galactose (ratio ~2:1), it is a bitter taste and it is not a sugar, a flavour or a flavour enhanced and it is not a sweetener. It is not used to improve palatability or other effects as such or during heating. It is an organic chemical with carbon, oxygen and hydrogen, the total combustion produces CO2 and H2O, but depending by the conditions of the combustion and interactions with other chemicals, environmental contaminants and nitrogen present in the atmosphere a large number of organic chemical can be present in combustion fumes, and some toxic chemical like aldehydes (formaldehyde or acetaldehyde) which are common by-products in combustion processes.This assumption is valid for all organic chemicals not depending by Guar Gum structure, but by the condition of combustion The evidences of some dangerous pyrolysis by-	

			products is not correlated to the specific use of guar gum in the condition of the test, but depending to the combustion conditions which is valid for all organic chemical (with all C-H-O structures). Finally after a deeply evaluation of the literature, at the moment no data (attached the reference of literature), based on scientific assessment, shows a real improvement of the tobacco toxicity after addition of Guar Guam, which is not an additive used as flavour or sweeteners to enhance the taste of tobacco smoke Considering the above considerations, the assumptions about Guar Gum appear not fully correct, starting from the concentration and quantity used as tobacco additive, and they does not support an increase of toxicity in tobacco combustion fumes,	
199.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.5.9 Guar gum	*Repetition of comment Nr 11*	Please see the answer to comment n°11.
200.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	2.5.9 Guar gum	*Repetition of comment Nr 11*	Please see the answer to comment n°11.

201.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	3 OPINION	p.66, l.16 and p.68, l.11-13 Please delete all the references regarding "attractiveness" as they are irrelevant. Please refer to our comment on p.4, l.16 +p.5 l. 8 p.66, l.32 It is crucial that the concept of "addictiveness" is adequately defined and that "addictiveness" is objectively measureable before it may be considered as a basis for regulation. p.66, l.33 Please amend as follows: "mechanisms underlying addictiveness are poorly understood." The mechanisms underlying "addictiveness" of the final tobacco product are not elucidated. p.66, l.36-39 Interactions of additives and their possible degradation products with tobacco constituents under the conditions of use have been reported for decades in the scientific literature and reported to authorities in form of regulatory submissions. SCHEER should not suggest that absolute criteria (Step 2) and should endorse the comparative testing to assess the effect of each additive and their pyrolysates under the actual condition of use. Please refer to our comment, p.4 l.39-46. p.66, l.44-46 According to SCHEER, the precautionary principle "stipulates that a reasonable suspicion of toxicity is sufficient to deny approval of such a substance" Please note that the TPD2 does not allude to the puzzling notion that a "reasonable suspicion" should be the basis for decisions about the use of additives. On the contrary, Articles 6(2) and 7(9) require such decisions to be based on concrete evidence, i.e., findings that an additive increases the "addictiveness" of a product "to a significant or measurable degree."	The comment has been accepted and the text has been modified accordingly. The definition is now included in the revised version, although it was clearly defined in Opinion I, in line with the SCENIHR 2010 document. Please see the previous answer to the pyrolysis comment (e.g. n° 72). The sentence on the application of the PP has been re-phrased to avoid inconsistencies with TPD and misinterpretations about risk management.

			p.67, l. 13-15 Please refer to our comment p.24 l. 1 –18 p.67, l.23-25 Please refer to DIN 2014, commenting that "The use of control cigarettes with varying specifications (e.g. tobacco blends) does not seem necessary. As can be seen from the literature, given additives have been tested with variable control cigarettes in several laboratories. Despite the use of different control cigarettes, comparisons between the control and the test cigarettes led to the same results." p.67, l.11-30 SCHEER's reasoning that comparative studies are "are not considered suitable" appear to be based on a fundamental misinterpretation of the TPD2. SCHEER's dismissal of comparative studies, looms to embrace the notion that, on many occasions, fluctuations in toxicity due to an additive are likely to be very small in comparison to the results that would be produced by pyrolysis of the final product without the additive, and therefore impossible to measure. Article 6(2) relies upon this distinction and is intended to ascertain when such an impact is measureable upon consumption of the final product, so that the prohibition in Article 7(9) can then be invoked. Please note that the wording of the TPD2, i.e., Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of	Please see answer n°1 to comment n°1 for CT.

			that additive in isolation. p.67, l.30 Please comment that pyrolysis study provides a gross overestimate of degradation products that might appear in cigarette smoke under smoking conditions. Please refer to our comment on p.4, l.39-46. p.67, l.37 Please remove "relevant and valid", replace by "tentative methods."	 Please see the previous answer to the pyrolysis comment (e.g. n° 72) The sentence has been changed.
202.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	3 OPINION	p.66, l.16 and p.68, l.11-13 Please delete all the references regarding "attractiveness" as they are irrelevant. Please refer to our comment on p.4, l.16 +p.5 l. 8 p.66, l.32 It is crucial that the concept of "addictiveness" is adequately defined and that "addictiveness" is objectively measureable before it may be considered as a basis for regulation. p.66, l.33 Please amend as follows: "mechanisms underlying addictiveness are poorly understood." The mechanisms underlying "addictiveness" of the final tobacco product are not elucidated. p.66, l.36-39 Interactions of additives and their possible degradation products with tobacco constituents under the conditions of use have been reported for decades in the scientific literature and reported to authorities in form of regulatory submissions. SCHEER should not suggest that absolute criteria (Step 2) and should endorse the comparative testing to assess the effect of each additive and their pyrolysates under the actual condition of use. Please refer to our comment, p.4 l.39-46. p.66, l.44-46 According to SCHEER, the	The comment has been accepted and the text has been modified accordingly. The definition is now included in the final Opinion, although it was clearly defined in Opinion I, in line with the SCENIHR 2010 Opinion. Please see the previous answer to the pyrolysis comment (e.g. n° 72). The sentence on the application of the PP has been re-phrased to

			precautionary principle "stipulates that a reasonable suspicion of toxicity is sufficient to deny approval of such a substance" Please note that the TPD2 does not allude to the puzzling notion that a "reasonable suspicion" should be the basis for decisions about the use of additives. On the contrary, Articles 6(2) and 7(9) require such decisions to be based on concrete evidence, i.e., findings that an additive increases the "addictiveness" of a product "to a significant or measurable degree." p.67, l. 13-15 Please refer to our comment p.24 l. 1 –18 p.67, l.23-25 Please refer to DIN 2014, commenting that "The use of control cigarettes with varying specifications (e.g. tobacco blends) does not seem necessary. As can be seen from the literature, given additives have been tested with variable control cigarettes in several laboratories. Despite the use of different control cigarettes, comparisons between the control and the test cigarettes led to the same results." p.67, l.11-30 SCHEER's reasoning that comparative studies are "are not considered suitable" appear to be based on a fundamental misinterpretation of the TPD2. SCHEER's dismissal of comparative studies, looms to embrace the notion that, on many occasions, fluctuations in toxicity due to an additive are likely to be very small in comparison to the results that would be produced by pyrolysis of the final product without the additive, and therefore impossible to measure. Article 6(2) relies upon this distinction and is intended to ascertain when such an impact is measureable upon consumption of the final product, so that the prohibition in Article 7(9) can then be invoked. Please note that the wording of the TPD2, i.e.,	avoid inconsistencies with TPD and misinterpretations about risk management. Please see the answer n°1 to comment n°1 for CT.

			Articles 6(2)(a), (d) and Article 7(9), include reference to the assessment of toxicity, addictiveness and CMR properties in the specific context "of the products concerned" or "a tobacco product at the stage of consumption." Thus, the purpose of the testing data provided pursuant to Article 6(2)(d) will be to allow the Commission to assess whether a given additive results in a significant or measureable increase in toxicity, addictiveness or CMR properties upon consumption of the final tobacco product, as opposed to the mere presence of those properties upon combustion of that additive in isolation. p.67, l.30 Please comment that pyrolysis study provides a gross overestimate of degradation products that might appear in cigarette smoke under smoking conditions. Please refer to our comment on p.4, l.39-46. p.67, l.37 Please remove "relevant and valid", replace by "tentative methods."	Please see the previous answer to the pyrolysis comment (e.g. n° 72) The sentence has been changed.
203.	Ureel, Ludwig, British American Tobacco, ludwig_ureel @bat.com, United Kingdom	3 OPINION	SCHEER has not provided comprehensive guidance on the type and criteria of testing to be carried out, despite this being the purpose of the Opinion. SCHEER also appears to have two conflicting views with regard to how the tests should be carried out. Whilst it wants studies to be "related to actual human exposure" (p. 67:8) it also claims that "the	The SCHEER disagrees with the comment. This is outside the remit of our mandate. The SCHEER was not asked to give detailed protocols but to advice the Commission on a possible framework to help the MS in asking and Tobacco Industry (TI) to present sound data; in particular the ToR states: *The Committee is asked to advise the Commission on the* ***type and criteria for comprehensive studies*** *that should be requested*. It has been clarified upfront in the text. Please see the answers to previous comment on the same topic.

			effects of the pure additive" are of importance. These views are at odds with one another, given that smokers are not exposed to the pure additive in isolation. Exposure to the pure additive in isolation does not conform to the requirement under Article 6 TPD2 that the test take into account the intended use of the product concerned.	
			SCHEER propose a stepwise approach which in principle we agree with, however it also states in 2.4.3.4. that "[t]here are hundreds of QSAR models, however the quality of reporting varies from model to model and predictivity must be assessed case by case." This undermines the stepwise model as the only way to assess predictivity of each model is by progressing the subsequent steps in the process.	Due to the different applicability domain typical for QSAR models, it is not possible to suggest a single fit for all models. Therefore the SCHEER reiterate that the most appropriate model should be evaluated on a case-by-case basis.
			The 18 month timeframe for reporting compliance to this article also means that a step-wise approach is not practically possible unless the 18 month timeframe can be used to address the in-silico and in-vitro tests only, with any further studies being allowed an extended timeframe for completion. In the absence of this all testing will need to be undertaken in parallel rather than series to meet the reporting deadlines.	This comment contradicts the many previous comments highlighting the bulk of data that TI has already produced to evaluate the safety of tobacco additives. SCHEER is not asking for any complex and long-term new testing.
			In the Opinion there is further ambiguity expressed regarding animal experimentation – in line 31 p67 the Opinion states "for ethical reasons, animal studies are not endorsed to assess the safety of a tobacco additive." However in key areas of the earlier parts of the document in-vivo approaches are proposed: Neurobiological effects using imaging techniques states that "additive effects on nicotine dependent activation….can be studied in-vivo…." (p.37:5)	The position of the SCHEER is quite clear and there is no contradiction. Please note that the SCHEER has indicated that in 'exceptional cases' in vivo studies can be agreed between TI and the Competent Authorities throughout the Opinion. Reference to in vivo testing has been made for addictiveness, for which in vitro testing is extremely limited.

			Behavioural responses in Rodents cites "animal models of nicotine administration…..as a reliable animal model with high predictive value for the dependence potential of a drug" (p.39:43) In its recommendations "The SCHEER therefore proposes to use a stepwise approach of 1) in silico, 2) in vitro, 3) ex-vivo, and 4 in-vivo methods – only in exceptional cases…" (p.40:41) It further clarifies those "exceptional cases" (p.40:45–p.41:1): "After negative results of testing….in the first method (in-silico), the next step should be considered…..(in-vitro), and so on."	
204.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	3 OPINION	Using DKFZ's proposal as a basis for SCHEER's opinion 2 is not consistent with Art. 7(9) TPD and should be replaced with a weight of evidence approach (see our comment re abstract). Therefore, we recommend to replace "The tiered (…) minimized." (p. 66, l. 16-19) with "The weight f evidence approach is proposed". In particular, stopping the evaluation of additives already at step 2, does not allow to assess whether an additive increases the toxic or addictive effects or the CMR properties as required by Art. 7(9) TPD. It is premature at step 2 to make TPD-compliant decisions (positive or negative) about the additive and the evaluation should always proceed to step 3. It follows that the phrase "In case (…) evaluation possible," (p. 66, l. 26-27) should be replaced with "In step 3,". Furthermore, we suggest to add after "validated." (p. 66, l. 35), "After completion of all three steps, the evidence obtained in all three steps should be assessed and weighted (weight of evidence approach)" (see our comment to 2.4). Similarly, if comparative testing strategies are excluded, it would not be possible to determine	Please see the answer(s) to the same comments by the same commenter regarding other parts of the Opinion.

			whether an additive increases the effects or properties as required by Art. 7(9) TPD. Therefore, we recommend to either delete the paragraphs "Furthermore, comparative (…) Section 3.4)." (p. 67, l. 11-30) completely or to adjust them to provide for comparative testing according to our more detailed comment on section 2.4.3.1). We suggest deleting the whole paragraph (p. 66, l. 40 – p. 67, l. 3). The recommendations on how to set the level of proof of safety and how to apply the precautionary principle in this paragraph go beyond SCHEER's mandate and are not in line with Art. 6 and 7 TPD (see in more detail our comments to section 2.1). Where no validated methods exist as, for example for the determination of pyrolysis products of tobacco additives (p. 66, l. 24-25 and p. 68, l. 21-22) or the assessment of addictiveness (p. 66, l. 32-33 and p. 68, l. 22) we encourage SCHEER to trigger the development of relevant research. We would welcome any opportunity to contribute to this research and method development. In the meantime, we will carry out and report on studies using the best currently available methods. Since attractiveness is not a relevant criteria under Art. 6 and 7 TPD, we suggest to delete all references to attractiveness, in particular ", as contributing to attractiveness of tobacco additives" (p. 66, l. 16), "contributing to attractiveness" (p. 68, l. 10-11) and "and attractiveness" (p. 68, l. 22). SCHEER is relying on SCENIHR's analysis of "major data gaps already identified in Tobacco Opinion 1 for the 15 additives". We disagree with this analysis and refer in this regard to our comment regarding	

			section 2.2. However, we agree that some knowledge gaps still exist. As already stated before, we encourage SCHEER to trigger the development of relevant research, in line with the Committee's expressed interest at p. 69, l. 25-26 ("It is advised that independent bodies or organisations begin conducting relevant research"). We would welcome any opportunity to contribute to this research and method development.	
205.	Thielen, Anja, Deutscher Zigarettenverband, a.thielen@zigarettenverband.de, Germany	3 OPINION	The report of SCHEER aims to present an approach for the assessment of tobacco additives. We have serious concerns on the scope, alleged findings and recommendations of the Preliminary Opinion and would like to raise some in-principle and critical remarks. SEE ATTACHMENT!  DZV_Konsultation_SCHEER_20160922.pd	Please see the previous answer(s) to the same comment(s).
206.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	4 MINORITY OPINION	The EU currently produces approximately 200,000 metric tons of raw tobacco annually, being the world's fifth largest producer after China, Brazil, USA and India (Nomisma Report 2012, DGAGRI/C.4 2016). About 300,000 persons are working in the tobacco growing sector in the EU with about 60,000 being growers/farms (DGAGRI/C.4 2016). Leaf processing is a major source of employment and income for the agro-industrial sector (Nomisma Report 2012). About 40 % of the tobacco produced in the EU is air-cured (Burley light air-cured, dark air-cured tobaccos), or sun-cured (Oriental tobaccos) (DGAGRI/C.2 2014). These tobacco types	This is outside the SCHEER mandate.

			are cultivated primarily by small-scale growers, often on family-owned farms. Such farms tend to be in locations where few alternative types of agriculture or few alternative forms of employment exist (Nomisma Report 2012). Additives are required in order to make most grades of Burley useable, in terms of quality and flavor, in the formulation of American Blend (AB) products, which also include Oriental and Virginia tobaccos. AB products represent over 80 % of the total volume of cigarettes in the EU (Euromonitor Intl. 2012). Any ban or excessive restriction on the use of additives could have the following negative consequences: manufacturers will not be able to use most grades of Burley tobaccos in the production of AB products. Thus, Virginia products would result in one of the few alternative products that could be manufactured without additives and still be acceptable by consumers. Virginia products do not require the inclusion of air-cured or sun-cured tobacco types. This in turn will de facto eliminate the need to use Burley and Oriental tobaccos, severely impacting 70-80 % of tobacco farmers in the EU (Nomisma Report 2012). The production of Virginia cigarettes requires the use of Virginia tobacco, and this is sourced exclusively from outside the EU. The conversion of Burley tobacco farms to Virginia tobacco farms would require significant investments in terms of curing barns that in the EU would be operated almost exclusively through the burning of fossil fuels (Nomisma Report 2012). However, due to the different climatic and soil conditions required in the cultivation of Burley and Virginia tobaccos, it is unlikely that currently Burley-growing areas could be converted to growing Virginia crops. Areas currently growing Oriental tobaccos (e.g. Bulgaria and Greece) could not be reconverted to growing Virginia tobaccos because of climatic conditions. In	

			terms of Virginia tobacco production, the majority of European farmers would not be in a position to achieve the competitiveness required to remain in the market. Models for alternative crop implementation across the EU have yet to be proven successful. For example, an EP-sponsored research project on alternatives to tobacco in Bulgaria was inconclusive; as a result, the EP itself recommended that Bulgarian growers remained in tobacco production (DGAGRI/C.3 2011). In addition, no economically viable alternatives to ca. 39,000 smallholder farmers growing Oriental tobaccos in Bulgaria and Greece have so far been identified. The majority of consumers in the EU prefer AB products; a ban on additives would encourage the supply of unregulated, illegal cigarettes of this style, resulting in an increase of illicit trade, undermining the anti-illegal trade efforts of national governments, law enforcement and tobacco manufacturers. Manufacturers would no longer be able to offer consumers a choice in taste style if production was to shift towards Virginia products only. This would create consumer confusion for those shifting from AB to Virginia products, and could further favor their uptake of contraband or counterfeit products.	
207.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	6 REFERENCES	Please note that we could not locate the following cites in the reference list provided by SCHEER, although they were mentioned in the text of this opinion. • Fowles 2001 • Wackowski and Delnevo 2015 • Brennan et al; • Nonnemaker et al. • Noriyasu et al. 2013 • Smith et al. 2014 • Ha et al. 2015	Thank you for pointing this out. The missing references have been added.

			• Alpert 2015	
208.	Stoddart, Gilly, PETA International Science Consortium Ltd., GillyS@piscltd.org.uk, United Kingdom	6 REFERENCES	On page 85, line 23, the cited author's name is spelled incorrectly. The correct spelling is Manuppello.	Thank you for the comment, the typo was corrected.
209.	Buch, Per, Mac Baren Tobacco Company A/S, per.buch@mac-baren.com, Denmark	7 Annex I	p.8 line 27-29,p13 line 11 ff, p 16 line 15 ,p 21 line 17 ff, p 23 section 2.4.2.3, p24 line 5ff p.25 line 26 ff  DK_-_SCHEER.docx	Please see the answer to comment n° 9.
210.	Martinez, Javier, JT International SA, 8 rue Kazem Radjavi, 1202 Geneva, Switzerland, Javier.Martinez@jti.com, Other	7 Annex I	p.97, l.30-p.98, l.12 "Attractiveness" is neither listed among the criteria for "comprehensive studies" in Article 6(2), nor is it mentioned in Article 7 as a basis on which Member States may prohibit the use of an additive. Thus, the Committee exceeds the TPD and its Terms of References when examining whether additives increase "attractiveness". The SCHEER precisely points to the only two references to "attractiveness" provided in the TPD2. Tellingly, these references clarify that the industry is not compelled to test for "attractiveness", and highlight the lack of any basis on which the Commission or Member States may take action with respect to "attractive" additives, except in the very limited context of additives that result in a characterizing flavor. Neither the SCHEER nor the Commission has authority to	Sometimes, the SCHEER uses the word attractive(ness) to clarify that this is the reason for the prohibition of cigarettes and roll-your-own with characterising flavours. On other occasions, it has been replaced by "properties facilitating inhalation or resulting in characterising flavour".

			amend the TPD. Consequently, the reference regarding "attractiveness" is irrelevant and should be removed.	
211.	Simms, Liam, Imperial Tobacco Limited, liam.simms@uk.imptob.com, United Kingdom	7 Annex I	Page 95, Lines 11-13: SCHEER should offer guidance on what is considered "verifiable justification" for requests for confidentiality treatment of information submitted as part of the dossier. Page 96, Lines 19-22: The provision of all raw data is considered to be an excessive requirement for an EU review of submitted studies. This requirement is over burdensome and the raw data will not be available in all cases. Imperial Tobacco believes that summary tables and appendices, where available, are more than sufficient for the external review purposes. Data from the published literature will have undergone a review process at the time of publication. Clearly if the required data is not available within the journal article it cannot be	The format for reporting is a guidance and could be adjusted by the Competent authorities. Assessors are usually civil servants obliged to confidentiality. There is no guidance that the SCHEER could provide. The SCHEER Opinions are per definition public, when the SCHEER is asked to treat information as confidential, the Opinion becomes more difficult to understand and vague because often product names and companies need to be coded. For this reason, the SCHEER needs to be able to verify that data deserves the status of confidentiality. In the past the SCHEER often found that data submitted with the request that it be treated as confidential could in fact be found on the internet or in published literature and thus confidentiality was not warranted. In order to reduce the workload of the SCHEER working group, any request for data confidentiality should be accompanied by the justification for this request. SCHEER clearly state in the Opinion the following: - If data is derived from an original study, all original (rough) data should be submitted - If data is derived from literature, the full paper/report should be submitted. This is fully in line with the comment. Please note that the availability of raw data for new studies is requested by Quality systems and should be available on requests in many different regulatory areas. TI should provide them, on request. Usually the Final Report is submitted. The SCHEER is aware that the availability of raw data for papers published in scientific journal is extremely limited.

			provided to the expert review committee. We support evidence based on robust methods and credible scientific research, on which valid assessment can be based.	The SCHEER is happy to read this statement.
212.	May, Anne, Philip Morris International Management SA, anne.may@pmi.com, Other	7 Annex I	On p. 95 l. 20 we suggest to add "…and/or IUPAC name" as the IUPAC name is typically used to identify chemicals. We suggest to specify for which temperature the vapor pressure should be reported p. 95 l. 35 & p. 96 l. 12. Since attractiveness is not a valid criterion under Art. 6 and Art. 7 TPD nor part of SCHEER's mandate, we suggest to delete on p. 98 l. 42 the word "attractiveness".	The comment has been accepted and the text has been modified accordingly. It is correct. Vapour pressure is strongly dependent on the temperature of the substance and should therefore be reported together with the vapour pressure. Most often vapour pressure is reported at relative normal ambient temperatures (20 or 25 °C). The text has been modified to indicate that temperature needs to be included. The comment has been accepted. Correct issue should read: 'CHARACTERISING FLAVOUR AND INHALATION FACILITATION PROPERTIES ASSESSMENT'. This has been changed in the Opinion.

Comments received by email

No.	Name of individual/organisation	Submission	SCHEERs response
1	Marshall Lindsay, Humane Society International, lmarshall@hsi.org, United Kingdom	Dear Sir/Madam, I have uploaded my comments on the web site as requested, but this did not allow me to include all the references that I had used in my response. Please would you accept this pdf of the entire response, on behalf of the Humane Society International. I would really appreciate it if you could acknowledge receipt of this document, as I know that the deadline for comments is today and I do not want to miss this opportunity. Many thanks,	Please see the SCHEER's previous answer to your comments on specific chapter(s) in the Opinion.

		Lindsay Marshall, PhD Science Communications Officer t +44 (0) 7719 531675 lmarshall@hsi.org<mailto:lmarshall@hsi.org> Humane Society International & The Humane Society of the United States 5 Underwood Street London N1 7LY United Kingdom  SCHEER Response Tobacco additives HS	
2.	Peter Van Der Mark peter.vandermark@esta.be	 ESTA Letter on the SCHEER Preliminary O Dear Sir/Madam, Please find attached a letter for your attention.	Please see the answers to previous comments on ToR, validated methods, CT and pyrolysis.