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EXPLANATORY NOTE FOR THE MODIFICATIONS OF THE SCENIHR OPINION ON ADDICTIVENESS AND ATTRACTIVENESS OF TOBACCO ADDITIVES FOLLOWING THE PUBLIC CONSULTATION ON THE PRE-CONSULTATION OPINION

This note sets out the rationale for the modifications made to the opinion of the European Commission Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) on Addictiveness and Attractiveness of Tobacco Additives following a public consultation conducted between 9 July 2010 and 5 September 2010.

Introduction

In March 2009, the European Commission requested the Scientific Committee on Emerging and Newly Identified Health Risks to assess the addictiveness and attractiveness of tobacco additives. A SCENIHR Working Group comprising four members of the SCENIHR and nine experts from academia with experience on the subject was formed. The WG produced a draft opinion which was discussed and adopted by the SCENIHR plenary on 6 July 2010 as a preliminary opinion suitable for public consultation (pre-consultation opinion).

In line with its procedures for stakeholder dialogue, implemented in the Rules of Procedures of the new Scientific Committees set up by Commission Decision 2008/721/EC of 5 September 2008, the European Commission Health and Consumers Directorate General (DG SANCO) conducted a public consultation on the pre-consultation opinion of SCENIHR between 9 July 2010 and 5 September 2010.

Results/participation

By the deadline, DG SANCO received a total of 31 contributions. All of them were reviewed by the Working Group during its meetings on 15 September, 5 October and 27 October. After introducing appropriate modifications, the opinion was adopted as the final opinion by the SCENIHR by written procedure on 12 November 2010.

Modifications to the opinion

The opinion has been modified to take into account all submitted comments which were assessed by the Working Group to be pertinent and relevant for the subject matter and which were within the competences of the Scientific Committees and respected the clear separation between risk assessment and risk management that underpins the Scientific Advisory structure of the European Commission. Comments on policy, risk management, legal clarification, the precautionary principle, were not considered as, although pertinent to the subject matter, they are outside the competences of the Scientific Committees.

Detailed explanations of the way the comments received were treated by the SCENIHR are provided below. The numbering of pages and sections correspond to the final opinion adopted by the SCENIHR on 12 November 2010 which is published together with this document. In addition, a new **chapter 5** has been inserted in the opinion to deal in general with the comments and changes (**pages 88-92**).

Revisions concerning the answer to question 1

Some comments inquired into the criteria chosen by the Commission to consider that tobacco is highly addictive. These come from different studies including epidemiological data. These data are now included in the opinion (**Section 3.1, page 15, Table 1**).

There was a disagreement regarding the terminology "weak" addictive potential of nicotine. This has been clarified by mentioning the weaker abuse liability of nicotine in animal studies when compared to the high addictive potential of tobacco products in humans. **Changes appear in the abstract (page 4-5), executive summary (point 1, page 9), conclusion section 3.16 (page 81) and opinion (chapter 4, point 1, page 82).**

Revisions concerning the answers to questions 4 and 5

It has been commented that self-administration of acetaldehyde in animals is not enough to suggest that sugars might be viewed indirectly as addictive themselves. Thus the phrasing has been modified, using the term potentially addictive, **in the executive summary (point 4, page 8) and opinion (chapter 4, point 4, page 83)**.

The SCENIHR agrees that the sentence indicating that "sugars, added in high quantities in most tobacco products" is not correct. Sugars are added to Burley tobacco to compensate for the loss of sugars during curing. This proves the importance of added sugars/inherent sugars for the flavour of the product. This final composition also explains why there is no significant difference between sugar-related pyrolytic end-products in the smoke from American blend and Virginia cigarettes. The formulation has now been changed into: "However, sugars, polysaccharides and cellulose fibres which are naturally present in tobacco, or sugars added in high quantities to most tobacco products, give rise to numerous aldehydes, such as acetaldehyde, in tobacco smoke." Changes appear in the **abstract (page 4-5)**, and, in a similar wording, **in the executive summary (point 4, page 9) and opinion (chapter 4, point 4, page 83)**.

Many comments indicate that there is little scientific evidence that acetaldehyde present in tobacco or tobacco smoke and produced by sugars pyrolysis is responsible for an increased addictiveness of nicotine through an inhibition of monoamine oxidases. Although it is undisputable that acetaldehyde is formed from sugar combustion and can inhibit monoamine oxidases, the SCENIHR agrees that it is not demonstrated that it is acetaldehyde contained in tobacco and tobacco smoke which is responsible for the decreased levels of monoamine oxidases observed in smokers' brain. Indeed, high levels of acetaldehyde are present in alcoholic patients but this acetaldehyde is oxidized by aldehyde dehydrogenase and drinking alcohol does not result in monoamine oxidases inhibition. The SCENIHR also agrees that there is no evidence that acetaldehyde produced by pyrolysis enters the brain through the smoke inhaled, although, in animal studies, acetaldehyde potently increases the rate of nicotine self-administration.

It is, however, clear that tobacco smoke contains compounds which inhibit monoamine oxidases. Aldehydes are intermediary products formed by monoamine oxidases which transform monoamines to organic acids and are therefore potent inhibitors of monoamine oxidases. Aldehydes are also "**al**cohol **dehyd**rogenated" compounds and can be formed through the combustion of poly-alcohols such as sugars. Acetaldehyde is not the only

aldehyde obtained following sugar combustion and the more complex aldehydes may as well inhibit monoamine oxidases. Moreover, their complexity would protect them from the action of the aldehyde dehydrogenase which oxidizes acetaldehyde. The role of these complex aldehydes arising from sugar combustion is now emphasized in the report. Changes have been made in the abstract **(page 4-5)**, **in the executive summary (point 4 and 5, pages 9-10) and opinion (chapter 4, point 4-5, pages 83-84).** The **section 3.8.1.4** has been partly rewritten to take into account the possible action of complex aldehydes in the inhibition of monoamine oxidases. Some new references are introduced to support the text. Please also note the section on research recommendations (3.15) which mentions that more research on this topic is required.

Concerning the many comments on menthol, **section 3.8.3.1** has been modified. It has been emphasized that menthol in smoke is 99% unchanged and a reference on this has been added. Included are also recent references to tobacco industry reviews claiming that menthol does not pose adverse health effects when used as an additive (Heck 2010, Werley et al. 2007). Another recent tobacco industry publication has been included reporting that menthol did not influence the metabolism of nicotine (Wang et al. 2010). However, the study was not designed to answer this specific question.

Some comments addressed smokeless tobacco and remarked that the additives used were not all found in the same products. In **section 3.8.4.4., page 57**, a sentence has been changed as follows to clarify the meaning: "More than 250 additives are found in different snus brands, most of them are flavours which are used in small amounts" In addition, the heading of **table 4, page 58** was changed to "The 50 additives present in greatest amount in different snus brands" and the title in column 2 changed to "Maximum percentage added to different snus brands". In **section 3.8.4.5, page 59**, a sentence was changed to "Most flavours are added in small amounts". In the same section, "no proof" has been replaced by "a lack of data".

Revisions concerning the answer to question 7

Some comments addressed the influence of technical characteristics on addiction. The meaning has now been clarified by the insertion of the following (or similar) sentence "The technical characteristics of cigarettes may thus modulate smoking behaviour but it is uncertain if this leads to a higher risk of addiction", **see abstract (page 4), executive summary (page 10), and opinion (chapter 4, point 7, page 84)**.

Revisions concerning the chapters on Gaps of knowledge, Research recommendations

Many comments addressed these sections, asking for being more specific or claiming that studies had already been done. The sections have now been rewritten in order to take into account the different proposals and appear in **sections 3.14 and 3.15**. The recommendations are also summarised at the end of the opinion (**chapter 4, pages 86-87**).

Various general comments

One comment underlined that the definition of cigars and cigarillos is not the same in Europe and in the US. In **section 3.3.1, page 18**, the definitions of cigars and cigarillos according to Council directive 2010/12/EU is now included.

In **section 3.4, page 22**, the explanation of casing is expanded and a reference included: (Akehurst 1981).

In **section 3.13.2, page 76** two sentences have been inserted stating "In Canada, the cigarette market consists almost exclusively of Virginia tobacco which is considered to

contain relatively few additives. It should be noted, however, that domestically manufactured "Virginia flue-cured cigarettes" from Canada are by no means "additive-free" (Hammond and O'Connor 2008)."

Several comments wanted to emphasize the harm reduction by changing from smoking to using smokeless tobacco. This aspect is out of scope of the current opinion but has been treated in the SCENIHR report from 2008. However, a recent study addressed this question and in section 3.8.4.4., page 57, the following paragraph was added:

"On the other hand, according to a recent study in the US, the promotion of smokeless tobacco as a safer alternative to cigarettes is unlikely to result in a substantial health benefit at a population level (Mejia et al 2010). The dual use of smokeless tobacco and cigarettes may in part explain the findings.

Other comments advocated the possible use of smokeless tobacco as smoke cessation aid, but as indicated in the SCENIHR report from 2008, the studies comparing the efficiency of smokeless tobacco with established therapies for smoking cessation are inconclusive. A phrase relating this aspect has also been inserted.

Comments for which no changes could be made

Comments regarding the answer to question 2

Several comments questioned the interpretation of the results in animals, claiming that there is no clear animal model of addiction.

Self-administration methods are commonly used to test the reinforcing properties of different products in animals. It has been found that evaluation of the reinforcing effect of a compound presents a high predictive value for the abuse liability in humans. Therefore, although these methods are not directly measuring the addictive effects of a compound, there is a consensus in the scientific community about the interest of such animal models in the study of addiction. Thus, the SCENIHR has used those results in a weight of evidence approach in combination with other scientific evidence.

Comments regarding the answer to question 3

Several contributors questioned the dose dependence of nicotine.

In the view of the SCENIHR, the pharmacological effects of nicotine, including its reinforcing effects, are dose-dependent. Similar to other drugs of abuse, an inverted U shape dose-response curve has been reported for the reinforcing effects of nicotine. This dose-response curve reveals:

a) The reinforcing effects of nicotine are directly dependent on the dose until reaching a maximum level.
b) After reaching this level, the reinforcing effects decrease also in a dose-dependent manner, probably due to the appearance of other pharmacological responses that include aversive effects. This decrease of the reinforcing effects has been also reported when using high doses of all the other drugs of abuse (i.e., cocaine, amphetamine, heroin, morphine, alcohol, cannabinoïds and others).

Claim: Non-Accumulation of nicotine in dependent smokers (chronic use of tobacco) (therefore no dose-dependency):

This is a misinterpretation. The SCENIHR is of the view that the lack of accumulation of nicotine in dependent smokers has no relationship with the dose-dependence of its pharmacological effects.

Claim: Receptor desensitisation (therefore, no dose-response effect):

This is also a misunderstanding. The well-reported desensitization of the nicotinic binding sites after repeated nicotine administration is not related to the presence or absence of dose-dependence in the pharmacological effects of nicotine. Indeed, other drugs of abuse that induce dose-dependent pharmacological effects also produce receptor desensitization (opioïds, psychostimulants, alcohol, cannabinoïds and others), which has been mostly related to the development of tolerance to their pharmacological responses.

Comment on genetic variation of receptors:

The SCENIHR is of the view that the literature cited in the text clearly reveals a linkage between genetic variations in the nicotinic acetylcholine receptors and the consumption of nicotine.

Comment on tolerance to nicotine:

The similar absorption and metabolism of nicotine in smokers and non-smokers were suggested in the comment to reflect a possible absence of pharmacokinetic tolerance. On the other hand, the development of physical dependence (presence of withdrawal symptoms) has been well reported in animal and human studies to be directly dependent on the dose of nicotine. Thus, the SCENIHR has concluded for a dose dependence to nicotine.

Comments regarding the answer to question 5

Two comments indicate that "*Berlin and Anthenelli 2001 acknowledge in that reference that it is a "hypothesis" that chronic habitual smoking can be understood in terms of reduced MAO activity. Berlin and Anthenelli also acknowledge in that paper that their conclusion that MAO inhibition by compounds found in tobacco smoke or tobacco can potentiate nicotine's effect is "speculation"*."

Although the SCENIHR agrees with this quotation it would like to note that Berlin and Anthenelli have written this comment in 2001 and since then many studies (2003-2009) have indicated the fundamental role of inhibitors of monoamine oxidases in the effects of tobacco. All the references are quoted in the opinion but, briefly, it has been shown that irreversible mixed A and B monoamine oxidases increase the serotonin cerebral extracellular levels and induce a desensitization of 5-HT1A receptors. This desensitization of raphe nucleus 5-HT1A receptors allows nicotine (i) to induce locomotor activity in mice, (ii) to be readily self-administered by rats and (iii) to uncouple noradrenergic and serotonergic neurons in mice. This latter finding indicates that a synergy between nicotine and inhibitors of monoamine oxidases can occur even if the pharmacokinetics of each compound is entirely different.

Comment: "The pharmacokinetic properties of acetaldehyde and nicotine are so different, that synergistic effects – particularly in the brain – are practically impossible."

The SCENIHR disagrees with this comment because if the MAO inhibition by aldehydes is irreversible, synergy may occur in spite of different pharmacokinetics .

Comment: "Discussions on ammonia have to be considered irrelevant since it is not used in the EU and ammonia is not on the common list of ingredients submitted to the European Commission (EC)."

This is not correct, because several salts with a buffering capacity (e.g. ammonium salts and phosphates) are used as tobacco additive in Europe.

Comments regarding the answer to question 7

One comment mentioned several scientific papers without submitting the full references. The working group managed to obtain some of these papers and evaluated them. The contradicting results from studies on puffing intensity and human smoking behaviour have been presented already. The same is true for the biomarker studies, the results for COHb, NNAL, nicotine equivalents have been presented already. The CYP2A6 polymorphism has been addressed elsewhere (section 3.6.1.5). One comment confirmed our statement about the function of TRPM8 and the interaction of menthol with this receptor. Further statements about the lack of interaction with other receptors seem not be relevant for the opinion.

Several comments draw the conclusion, that the inconclusive data mentioned in the opinion would be proof for the lack of evidence.

This is not the view of the SCENIHR, however, who wish to stress that inconclusive data are precisely that (i.e. inconclusive) and do not allow a statement regarding the weight of the evidence.

One comment made reference to the recent NCI bibliography on menthol and tobacco and compared the 340 references with the smaller number used in the opinion.

The SCENIHR has reviewed a large number of scientific publications but has used only the most relevant in the elaboration of its opinion. Thus, the reference list cannot be exhaustive. In the mentioned section, this is illustrated by the following example where the inhibition of nicotine metabolism by menthol was shown with results of the Benowitz et al. (2004) study. This study had been performed in a clinical setting with the i.v. application of deuterated nicotine and deuterated cotinine. Therefore the possibility of inhibition could be determined more precisely than in numerous field studies comparing nicotine metabolite excretion from smokers of mentholated and non-mentholated cigarettes (e.g. Wang et al. 2010).

Comments regarding the answer to question 8

Comments on: Definition of "attractiveness" and ability to measure this reliably

Response: The broadness of the term "attractiveness" is acknowledged in the report. Industry terms such as "acceptability" and "preference" have more specific meaning, but capture only part of what constitutes the attractiveness of a product. The role of sensory and environmental cues is already acknowledged.

Role of menthol in initiation

One comment discussed the percentage of smokers of menthol cigarettes in different ethnic groups in the USA. Unfortunately, no full reference was given, therefore an evaluation of the study was not possible. However, the figures from the USA show that 25-30% of the cigarettes purchased in the USA are mentholated brands. However, the SCENIHR acknowledges in its opinion that there is conflicting evidence regarding the specific impact of menthol on smoking behaviour.

Comments regarding the answer to question 9

Comments on availability of standard methods for assessing attractiveness

The lack of standardised methods for assessing attractiveness in the context of tobacco products is already acknowledged in the report, although the basic principles of how to assess subjective ratings are well established in behavioural science. Greater consistency across studies which investigate these factors would be welcome.

Comments on use of survey/market data and industry documents to assess attractiveness

Survey and market data may provide useful information, but any relationships between, for example, market share and the presence or absence of additives will be minimally informative due to the potential for multiple confounding influences, and cross-country differences in "national taste" etc.

Comments on ethical considerations in study of additives

While studies on the presence or absence of additives on smoking behaviour in established smokers may be ethically acceptable, these will be minimally informative with respect to effects on initiation. It would generally be regarded to be unacceptable to present tobacco (with or without additives), a harmful product with high addiction liability, to tobacco naive participants.

Comments regarding the answer to question 11

One comment stressed that lack of difference in the success rates in smoking cessation for persons who did or did not, respectively, smoke menthol cigarettes should prove that menthol cigarettes do not cause increased addiction.

In its opinion, the SCENIHR emphasizes that menthol may make it easier to begin smoking, among other things due to the effect of menthol on the lung system and that menthol may increase the uptake of nicotine and thereby cause a faster addiction. This is a situation completely different from that of smoking cessation where many psychological and social parameters interact.

As to the proposal that menthol should result in a lower consumption of cigarettes and that menthol cigarettes should be less attractive, this conclusion cannot be made based on the comparison of consumption between Americans of African ancestry and Americans of European ancestry. Many other parameters decide how large the consumption of cigarettes is in a population.

Miscellaneous comments

Regarding the comment(s) on sugar added to smokeless tobacco it was stated that no sugar is added to Swedish snus. However, according to the data from the industry

website (**table 4, page 58**), maltodextrin is added at a maximum of 1.4% and invert sugar at 0.2%. In addition, liquorice (added up to 1.1%) has a sweetening capacity higher than sucrose. These quantities are less than those used in certain American blend tobaccos but they are not insignificant.