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Review of industry reports on EU priority tobacco additives part A: Main outcomes and conclusions

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ABSTRACT

The European Union Tobacco Products Directive (EU TPD) mandates enhanced reporting obligations for tobacco manufacturers regarding 15 priority additives. Within the Joint Action on Tobacco Control (JATC), a review panel of independent experts was appointed for the scientific evaluation of the additive reports submitted by a consortium of 12 tobacco manufacturers. As required by the TPD, the reports were evaluated based on their comprehensiveness, methodology and conclusions. In addition, we evaluated the chemical, toxicological, addictive, inhalation facilitating and flavoring properties of the priority additives based on the submitted reports, supplemented by the panel's expert knowledge and some independent literature. The industry concluded that none of the additives is associated with concern. Due to significant methodological limitations, we question the scientific validity of these conclusions and conclude that they are not warranted. Our review demonstrates that many issues regarding toxicity, addictiveness and attractiveness of the additives have not been sufficiently addressed, and therefore concerns remain. For example, menthol facilitates inhalation by activation of the cooling receptor TRPM8. The addition of sorbitol and guar gum leads to a significant increase of aldehydes that may contribute to toxicity and addictiveness. Titanium dioxide particles (aerodynamic diameter <10 µm) are legally classified as carcinogenic when inhaled. For diacetyl no report was provided. Overall, the industry reports were not comprehensive, and the information presented provides an insufficient basis for the regulation of most additives. We, therefore, advise MS to consider alternative approaches such as the precautionary principle.

ABBREVIATIONS CMR: carcinogenic mutagenic reprotoxic; COPD: chronic obstructive pulmonary disease; EC: European Commission; EU: European Union; EU-CEG: European Common Entry Gate; IARC: International Agency for Research on Cancer; JATC: Joint Action on Tobacco Control; NIOSH: National Institute for Occupational Safety and Health; MAO: monoamine oxidase; MS: Member State; MSS: mainstream smoke; RYO: roll your own; SCENIHR: Scientific Committee on Emerging and Newly Identified Health Risks; SCHEER: Scientific Committee on Health, Environmental and Emerging Risks; SCOEL: Scientific Committee on Occupational Exposure Limits; TiO₂: titanium dioxide; TobReg: WHO Study Group on Tobacco Product Regulation; TPD: Tobacco Products Directive 2014/40/EU; TRPM8: transient receptor potential cation channel melastatin 8

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INTRODUCTION

In 2014, the European Tobacco Products Directive (TPD, 2014/40/EU)¹ entered into force. This directive lays down harmonized regulations regarding the manufacture, presentation and sale of tobacco and related products. Among other things, it concerns the regulation of ingredients and indicates that MS shall prohibit the placing on the market of tobacco products containing ingredients that

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result in a characterizing flavor, facilitate inhalation or nicotine uptake or lead to the formation of compounds with CMR (carcinogenic, mutagenic, or reprotoxic) properties¹ (Article 7). Moreover, it requires tobacco manufacturers to report to European Union (EU) member states (MS) on the ingredients used in their products. It also describes enhanced reporting obligations for additives included in a priority list² (Article 6). This list, currently containing 15 additives, was developed by the European Commission (EC) based on a previous assessment by the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR)^{3,4}.

Information about marketed tobacco products and their ingredients is submitted by manufacturers or importers to the European Union Common Entry Gate (EU-CEG) for each MS. A recent study using EU-CEG data from 12 EU MS showed that, on average, 12.7% of cigarette ingredients and 18.4% of RYO tobacco ingredients were reported to be priority additives⁵. The most frequently notified priority additive among cigarettes was titanium dioxide (23847 notifications), followed by cocoa, guar-gum, propylene glycol and glycerol (>10000 notifications each). For RYO, the most frequently reported priority additive was propylene glycol (1604 notifications), followed by glycerol and cocoa (980 and 681 notifications, respectively).

For the priority additives, manufacturers were required to submit reports based on comprehensive studies that examine for each additive whether it contributes to, and increases the toxicity and/or addictiveness of cigarettes or RYO tobacco to a significant degree. Moreover, studies had to be carried out to examine whether the additive results in the abovementioned properties (i.e. characterizing flavor, facilitation of inhalation or nicotine uptake, or formation of CMR compounds)¹. The provided information should help the EC and EU MS regulate tobacco products and ingredients based on Article 7 of the TPD. In response to the enhanced reporting requirements, a consortium of 12 tobacco manufacturers has submitted reports on 14 out of the 15 priority additives. No report was provided for diacetyl⁵, even though this ingredient was reported as a priority additive in 7 out of 12 MS in 2019⁵. The tobacco industry consortium published a synthesis of these reports in three journal articles⁶⁻⁸.

According to TPD Article 6, the EC and MS may require these reports to be peer-reviewed by an independent scientific body, particularly regarding their comprehensiveness, methodology and conclusions¹. The aim of this policy report is to summarize the outcomes of the assessment of the independent scientific body, during their assessment of the comprehensiveness, methodology and conclusions of the tobacco industry reports, as required in TPD Article 6.4. This article presents the primary outcomes and conclusions of our review of the industry reports and specific recommendations for the priority additives, and should be read in tandem with Part B, which describes the methodological shortcomings identified by our panel, that were common to all the industry reports.

EVALUATION OF INDUSTRY REPORTS

In October 2017, the Joint Action on Tobacco Control (JATC) was launched as a collaborative action between the EC and the MS to provide support for the implementation of the TPD in all MS. Within this JATC, Work Package 9 (WP9: *Additives Subject to Enhanced Reporting Obligations*) had the specific objective to support MS in evaluating data submitted regarding the enhanced reporting obligations for priority additives.

To facilitate the peer review of the submitted industry reports, an independent review panel of 10 international experts with expertise in various relevant areas was established. These reviewers worked together with several members from JATC partner institutes. The outcomes presented in this article reflect the opinions of the review panel and the involved partners⁹. In addition, we evaluated the chemical, toxicological, addictive and flavoring properties of each of the priority additives, based on the information presented by the industry, supplemented with our expertise and knowledge of independent research (i.e. without the involvement of the tobacco industry).

General concerns and review panel conclusions

Quality of the Industry reports

Regarding overall structure

Generally, the industry reports contain a summary, followed by chapters with overviews of the study designs and findings, then by many annexes with

the detailed methodology and results. Each report contains approximately 150–200 pages of main text and over 2000 pages of appendices. The report for titanium dioxide is substantially shorter, as it lacks several assessments (see PART B, Bolling et al.¹⁰). The submitted reports are not clearly structured, with many crossing references to annexes and appendices, some of which also have appendices. Some annexes and appendices that are referred to are missing. This unclear structure significantly hindered the scientific evaluation of the reports.

Regarding comprehensiveness, methodology and conclusions

Although, relevant topics are covered in the industry reports, essential aspects are missing in the assessment of most of the additives. In addition, as described in Bolling et al.¹⁰, the scientific quality of the reports is not sufficient, and therefore we concluded that they are not comprehensive. The insufficient quality was due to limitations in the applied methodology, for instance in the literature reviews, the toxicological and chemical evaluation, the statistical approach, and the assessment of inhalation facilitation, nicotine uptake, addiction and characterizing flavors. The aspects that were not addressed or were of insufficient scientific quality are discussed in Bolling et al.¹⁰.

Since we considered the scientific quality of the reports and the applied methodology insufficient, we question the scientific validity of the conclusions in the industry reports and conclude that these are not warranted.

Interpretation and ambiguity of the TPD

The interpretation of the TPD presented in the industry reports differs from our interpretation. This appears to be due to the ambiguity of the wording in Article 6.2.a and the conflicting content of Articles 6.2.a and 7.9. For a detailed description of the discrepancy between the two interpretations of the TPD, see Bolling et al.¹⁰. In short, we based our evaluation on Article 6 only, and consequently assessed the evidence for: a) the additive contributing to toxicity or addictiveness, and b) the additive increasing the effect size of the endpoint studied (toxicity or addictiveness). However, the industry assessed the evidence for b) only and used Article 7.9 as an argument for a comparative testing approach

since regulatory actions by the MS are required if an additive increases the toxic or addictive effect to a significant or measurable degree. We disagree that Article 7 is a valid argument for relying only on comparative testing for the chemical and toxicological analysis. This is supported by the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) opinion regarding the limited validity of the comparative testing approach^{11,12}. Thus, in our opinion, further data are required to fulfil the reporting obligations specified in Article 6 of the TPD. Moreover, a future revision of paragraphs 6.2 and 7.9 of the TPD is necessary for an unambiguous interpretation of the TPD.

Concerns regarding additives

The industry concluded that none of the additives in the tested application levels is associated with concern when used in cigarettes or RYO tobacco. However, we question the validity of this conclusion due to the poor scientific quality of the submitted reports. Despite the limitations in the industry reports, we have identified concerns regarding several additives and their properties based on the submitted information and our expert knowledge of independent research. These concerns do not represent an exhaustive list of all those possibly associated with the use of these additives in cigarettes or RYO tobacco. Table 1 provides an overview of the comparison between the industry's and our assessments. The following sections describe our main concerns regarding additives, grouping those with similar properties.

Menthol and geraniol

Menthol is a natural compound found in several plants of the mint family, e.g. peppermint, corn mint and spearmint, but is also produced synthetically. It imparts a minty taste and smell and has a characteristic cooling effect. Menthol is widely used in the food, flavor, oral hygiene, cosmetic, and pharmaceutical industries, and is also one of the most commonly used additives in cigarettes, RYO, and other tobacco and related products¹¹. Geraniol is a monoterpene alcohol with a rose-like aroma. It is also used as a flavoring agent in food and as a fragrance in cosmetics, and as an additive in tobacco products^{11,13}.

According to the TPD (Article 7.1), cigarettes and RYO tobacco products that have characterizing

Table 1. Overview of outcomes of the submitted industry reports as assessed by the Independent Panel

Additive	As provided in industry reports				Industry conclusion					Review panel's assessment of provided (and independent) data					
	Tested application level	Volatile?	Transfer rates	Main pyrolysis products	Chemical analysis: overall effect	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor	Chemical analysis, re-eval.: carbonyl comp.	Chemical analysis, re-eval.: other comp.	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor
Review panel's general remarks (see Chapter 4)			Only assessed for: cocoa, geraniol, glycerol, guaiacol, licorice, maltol, menthol, propylene glycol, TiO ₂	No new experiments were performed	Limitations in methodology (e.g. statistical analysis by industry was likely to cause false negative results)	Limitations in methodology (e.g. study design was not sufficient to evaluate CMR prop.)	Limitations in methodology (e.g. important Endpoints on dependence potential were not assessed)	Limitations in methodology (e.g. only descript. statistics were provided for smoking behavior param.)	Only assessed for: Carob bean, cocoa, fenugreek, fig, geraniol, guaiacol, licorice, menthol. Limitations in methodology	Review panel considers industry assessment as insufficient (see Chapter 4). Thus, evidence from independent literature was used when available, but no comprehensive literature review was performed. The review panel performed an evaluation of hazard classification of pyrolysis products. For MSS chemical analysis, usefulness of data provided by industry was limited (e.g. only ISO smoking regime was used, pyrolysis products were not included in analyte list, high standard deviations for some experiments), thus a re-analysis of the chemical data was performed by the review panel. For the remaining endpoints, addressed concerns are exemplary. Further details are given in the individual additive reports.					
Carob bean	Low 0.2% Max 0.4% Max-plus 0.6%	Carob bean is a complex mixture of mainly non-volatile compounds	Unknown but unlikely	Acetic acid (24.5%), acetol (3.4%), furfural (1.5%), pyruvaldehyde (1%); diluent propylene glycol was found at 65.4%	No statistically significant overall effect	No effect	No effect	No effect	No effect	No increase of carbonyl emissions at tested levels.	No additive-level related MSS effects in industry study. (Effects on MSS described in literature).	Pyrolysis product furfural has CMR properties, not followed up in MSS analysis.	Potential MAO inhibition has not been addressed.	Potential alteration of smoke pH has not been addressed.	Impact on tobacco flavor has likely been underestimated.
Cocoa	Low 0.5% Max 1.0% Max-plus 1.5%	Cocoa is a mixture, some components are volatile	Varies	Acetic acid (27.2%), acetol (6.6%), furfuryl alcohol (6.6%), caffeine (4.0%), pyrrole (2.8%), furfural + cyclopentanone (2.1%), phenol (1.6%) cresol + pyridenediol (1.4%), 2-butanone (0.9%), toluene (0.7%), styrene (0.2%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	No increase of carbonyl emissions at tested levels.	Additive level-related increase of cadmium	Pyrolysis product furfural has CMR properties, not followed up in MSS analysis.	Potential MAO inhibition has not been addressed.	Potential alteration of smoke pH has not been addressed.	Impact on tobacco flavor has likely been underestimated.
Fenugreek	Low 0.01% Max 0.02% Max-plus 0.03%	Fenugreek extract is a complex mixture, main components are not volatile	Unknown, but unlikely for main constituents	Ethyl linoleate (37.4%), ethyl palmitate (14.8%), ethyl stearate (10.6%), palmitic acid (6%), hydroxydimethylfuranone (3.4%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	No increase of carbonyl emissions at tested levels.	No additive-level related MSS effects in industry study.	Pyrolysis products (furfural, benzene, toluene, 2-butenal) have CMR properties, some were not followed up in MSS analysis.	Potential MAO inhibition (due to combustion of sugars) has not been addressed. However, application level is very low.	Potential alteration of smoke pH has not been addressed. However, application level is very low.	Impact on tobacco flavor has likely been underestimated.
Fig	Low 0.025% Max 0.15% Max-plus 0.30%	Fig juice concentrate is a complex mixture, main components are not volatile	Unknown, but unlikely for main constituents	Acetic acid (45.1%), furfural (24.5%), sorbic acid (10.2%), butanediol (3.7%); unknown emission (8.6%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	No increase of carbonyl emissions at tested levels.	No additive-level related MSS effects in industry study.	Pyrolysis product furfural has CMR properties, not followed up in MSS analysis.	Potential MAO inhibition (due to combustion of sugars) has not been addressed.	Potential alteration of smoke pH has not been addressed.	Impact on tobacco flavor has likely been underestimated.

Continued

Table 1. Continued

Additive	As provided in industry reports				Industry conclusion					Review panel's assessment of provided (and independent) data					
	Tested application level	Volatile?	Transfer rates	Main pyrolysis products	Chemical analysis: overall effect	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor	Chemical analysis, re-eval.: carbonyl comp.	Chemical analysis, re-eval.: other comp.	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor
Geraniol	Low 0.015% Max 0.030% Max-plus 0.045%	Yes	7-8%	Citral (4.6%), beta-myrcene (3%), ocimene (1.8%), neryl acetate (1.3%), alloocimene (0.7%), menthatriene (0.5%), limonene (0.4%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	Low quality of data does not allow conclusion.	Increase of nitrogen oxides, but quality of data low.	Increase in toxicity is unlikely (given the low application level), but cannot be excluded.	Not adequately assessed: only as part of a mixture.	Not adequately assessed: only as part of a mixture. Activation of the TRPM8 receptor was not addressed.	Impact on tobacco flavor has likely been underestimated.
Glycerol	Low 2.5% Max 5.0% Max-plus 6%	No	4.5% (in the literature up to 8%)	Glycerol (99.8%)	Decrease of benzo[a]pyrene, NAB, catechol, hydroquinone, m+p cresol, o cresol, phenol, quinoline. Increase of glycerol.	No effect	No effect	No effect	Not assessed	No increase of carbonyl emissions at tested levels.	Additive level-related increase of ammonia and water.	Industry's assessment insufficient.	Industry's assessment insufficient. However, no previously identified concerns regarding addictiveness.	Inhalation facilitation due to humidification not addressed.	No such effect expected.
Guaiacol	Low 0.0005% Max 0.001% Max-plus 0.0015%	Yes	Unknown	Guaiacol (92.5%), guaiacol acetate (6.3%), indanone (0.7%), dimethoxybenzene (0.3%), chinnoline (0.2%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	Low quality of data does not allow conclusion.	No additive-level related MSS effects in industry study (MSS effects described in literature).	Irritative effects have not been addressed. However, application level is very low.	Industry's assessment insufficient. However, no previously identified concerns regarding addictiveness.	Anesthetic effects are not assessed. However, application level is very low.	Impact on tobacco flavor has likely been underestimated.
Guar gum	Low 0.5% Max 1.0% Max-plus 1.5%	No	Not applicable	Hydroxymethylfurfural (13.4%), acetal (11.9%), acetic acid (9.9%), methyl pyruvate (6.1%), furfural (6.0%), cresol (0.9%), benzene (0.7%), 2-butanone (0.7%), toluene (0.5%), 2-butenal (0.2%)	Increase of formaldehyde and cadmium.	No effect	No effect	No effect	Not assessed	Almost all carbonyls increase with guar gum concentrations. The increase in formaldehyde is seen as significant and relevant.	Substantial variations of water and nitrogen oxides have not been explained by industry (MSS effects described in literature).	Pyrolysis products (furfural, benzene, toluene, 2-butenal) have CMR properties, some were not followed up in MSS analysis.	Not adequately assessed: only as part of a mixture. MAO inhibitors (aldehydes) were increased in MSS.	Not adequately assessed: only as part of a mixture. Potential alteration of smoke pH has not been addressed.	Influence of guar gum and its pyrolysis products on odor and taste was not assessed.

Continued

Table 1. Continued

Additive	As provided in industry reports				Industry conclusion					Review panel’s assessment of provided (and independent) data					
	Tested application level	Volatile?	Transfer rates	Main pyrolysis products	Chemical analysis: overall effect	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor	Chemical analysis, re-eval.: carbonyl comp.	Chemical analysis, re-eval.: other comp.	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor
Licorice	Low 0.6% Max 1.2% Max-plus 1.8%	Licorice is a mixture, most components are not volatile	Not applicable	Acetic acid (42%), acetol (11.9%), furfuryl alcohol (11.7%), diacetyl (4.1%), acetol acetate (2.0%), phenol (1.4%), cresol (0.2%), pyridine/pyrrole (0.2%), furfural (0.2%)	No statistically significant overall effect	No effect	No effect	No effect	No effect	No increase of carbonyl emissions at tested levels.	Increase of cadmium (MSS effects described in literature).	Pyrolysis products (furfuryl alcohol, phenol, furfural, diacetyl) have CMR properties or cause obstructive lung injury, some were not followed up in MSS analysis.	Potential MAO inhibition (due to combustion of sugars) has not been addressed.	Potential alteration of smoke pH has not been addressed.	Impact on tobacco flavor has likely been underestimated.
Maltol	Low 0.005% Max 0.01% Max-plus 0.015%	Not very volatile in ambient conditions	4.3–5.2%	Acetoxymethyl pyranone (0.2%); maltol transfers mostly intact	No statistically significant overall effect	No effect	No effect	No effect	Not assessed	Low quality of data does not allow conclusion.	Additive level-related increase of nitrogen oxides.	Increase in toxicity is unlikely (given the low application level), but cannot be excluded.	Not adequately assessed: only as part of a mixture. GABAA receptor inhibition has not been addressed.	Not adequately assessed: only as part of a mixture.	Influence of maltol on odor and taste was not assessed.
Menthol	Low 0.1% Max 1.2% Max-plus 1.8%	Yes	9.1–11.1% (in the literature up to 30%)	Menthone (0.9%), menthene (0.1%); menthol transfers mostly intact	Increase of menthol	No effect	No effect	No effect	Characterizing flavor at 1.2% or higher application	No increase of carbonyl emissions at tested levels.	Increase of NAT (MSS effects described in literature).	Indirect effects on toxicity (e.g. due to increased puff volume) have not been addressed.	Effects of menthol on addictiveness (e.g. alteration of nicotine levels, masking of aversive sensory experiences, serving as conditioned cue) have not been addressed.	Menthol’s ability to facilitate inhalation via activation of the TRPM8 receptor was not addressed.	Contrary to already existing literature. Effect on palatability and attractiveness due to cooling effect has not been addressed.
Propylene glycol	Low 2.5% Max 5.0% Max-plus 6%	No	Below 1% (in the literature 7.3–8.8%)	1,3-Propylene glycol (6.2%), acetol or acetic anhydride (4.7%), pyruvaldehyde (2.8%); propylene glycol transfers mostly intact	Decrease of m+p cresol and phenol. Increase of propylene glycol.	No effect	No effect	No effect	Not assessed	Low quality of data does not allow conclusion.	Increase of cadmium and additive level-related increase of nitrogen oxides.	Pyrolysis product pyruvaldehyde has CMR properties, not followed up in MSS analysis.	Industry’s assessment insufficient. However, no previously identified concerns regarding addictiveness.	Inhalation facilitation due to humidification not addressed.	No such effect expected.

Continued

Table 1. Continued

Additive	As provided in industry reports				Industry conclusion					Review panel's assessment of provided (and independent) data					
	Tested application level	Volatile?	Transfer rates	Main pyrolysis products	Chemical analysis: overall effect	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor	Chemical analysis, re-eval.: carbonyl comp.	Chemical analysis, re-eval.: other comp.	Toxicity	Addictiveness	Inhalation facilitation	Characterizing flavor
Sorbitol	Low 0.6% Max 1.2% Max-plus 1.8%	No	Not assessed	Furfural (31.4%), propylfuran (9.7%), acetylfuran (7.7%), furanone (6.4%), methoxycyclopentenone (5.2%)	Increase of acrolein and formaldehyde.	No effect	No effect	No effect	Not assessed	Relevant increase in carbonyl formation (esp. acrolein and formaldehyde) is attributed to additive.	Additive-level related increase of cadmium.	Increase of toxic carbonyls. Pyrolysis product furfural has CMR properties, not followed up in MSS analysis.	MAO inhibitors (aldehydes) were increased in MSS.	Inhalation facilitation due to humidification not addressed.	Influence of sorbitol and its pyrolysis products on odor and taste was not assessed.
Titanium dioxide	0.5 mg per cigarette filter (not tested)	No	Not assessed	Not applicable	No comparative testing	Not assessed	Not assessed	Not assessed	Not assessed	No comparative testing	Insufficient evaluation of transfer of titanium dioxide to smoke.	EU Carc. 2 classification of titanium dioxide.	Not assessed	Not assessed	Not assessed
Diacetyl	No report provided									The inhalation toxicity of diacetyl and the development of obstructive lung diseases after exposure to it are concerns. Furthermore, as a flavoring, diacetyl could increase attractiveness of tobacco.					

General information about the 15 additives as provided in the industry report (grey columns: Low, Max and Max-plus application levels as targeted levels, a remark about volatility of the additive, transfer rates and pyrolysis products as provided in the industry reports); Industry's conclusion regarding influence of the 15 additives on smoke chemistry, toxicity, addictiveness, inhalation facilitation, and characterizing flavor (red columns); Review panel's assessment of the additives' influences on smoke chemistry, toxicity, addictiveness, inhalation facilitation, and characterizing flavor on the basis of provided data and independently performed literature searches (blue columns). For independent assessment of the industry's chemical analysis, the criteria described in Chapter 3 of Deliverable 9.3 were applied⁹. The addressed concerns in this table are only exemplary, more details are provided in the deliverable. Furthermore, some limitations and shortcomings of the industry's approach are briefly summarized under 'General remarks'. A more extensive discussion on this topic is given in Chapter 4 of Deliverable 9.3⁹.

flavors such as menthol or vanilla are prohibited. In the case of products with more than a 3% market share, such as menthol cigarettes, this ban applies as of May 2020. The sensory assessment provided by the industry showed that tested cigarettes with a menthol content of 1.2% had a characterizing flavor, as opposed to the other tested concentration of 0.6% of menthol. However, this finding should be treated with caution as we identified severe limitations in the applied methodology¹⁰. Noticeably, independent authors have reported that menthol imparts a noticeable flavor at 0.1–1%¹⁴. Menthol is currently used in cigarettes in amounts up to the reported threshold for a characterizing flavor of 1.2%, as reported to the Dutch section of the European Common Entry Gate (EU-CEG, accessed on 21 April 2021).

Main concerns

Inhalation facilitation and nicotine uptake

The industry concluded that menthol and geraniol do not facilitate inhalation or nicotine uptake. However, several independent studies indicate the opposite. For example, Ha et al.¹⁵ showed an increase in the nicotine metabolite cotinine in blood plasma of mice exposed to cigarette smoke containing l-menthol versus mice the exposed to reference cigarette smoke. Dunér-Engström et al.¹⁶ showed that menthol stimulates salivary flow, which might increase the dissolution of nicotine in the mouth. Moreover, Squier et al.¹⁷ demonstrated that menthol increases penetration of nicotine and carcinogenic nitrosonornicotine across oral mucosa and concluded that menthol increases the nicotine uptake.

Menthol is used as an anti-tussive compound in pharmacology (for review, see Dicipinigitis et al.¹⁸ and Eccles et al.¹⁹) and was shown to suppress strong irritancy induced by pro-tussive compounds in mice, dependent on activation of the transient receptor potential cation channel melastatin 8 (TRPM8), the cooling receptor²⁰. Similar effects had been found in guinea pigs²¹. Menthol was further shown to reduce cough sensitivity to inhaled capsaicin and improve inspiratory flow in chronic cough patients²².

The industry notes that it has not yet been explored whether geraniol can reduce the harshness of smoke and promote inhalation of irritating aerosols but did not present any new assessments.

However, geraniol is also an agonist of the TRPM8 receptor and thus may have similar effects to menthol when inhaled²³. Although this activity is comparatively weak in relation to menthol²³, activation of TRPM8 is an intrinsic physiological property of both substances, and combined exposures to several agonists of the TRPM8 receptor may result in additive or synergistic effects on receptor activation. Further, administration of geraniol in an animal model suppressed mediators of pulmonary inflammation²⁴ and alleviated asthma²⁵.

Although the industry describes the pharmacological properties of menthol, some key-publications that refer to menthol's intrinsic property to enhance inhalation are not adequately discussed (e.g. Willis et al.²⁰, McKemy et al.²⁶, Yerger et al.²⁷, and Ha et al.¹⁵). Two of these publications link TRPM8 activation by menthol to an improved sensation of breathing and air-flow, especially under conditions of respiratory diseases or toxicant exposure^{15,20}. The industry statement 'currently there is no published data in the literature which has investigated the relationship between the cooling sensation properties and facilitation of deeper inhalation' (Report for priority additive menthol, p.27⁵) implies deeper inhalation as a crucial criterion for facilitated inhalation. However, we argue that re-normalization of breathing patterns that are delayed or inhibited by toxicants is much more relevant, and this effect was confirmed for menthol and other TRPM8 agonists²⁰.

Menthol has been suggested to hardly affect smoking behavior and toxicant exposure of experienced smokers who are adjusted to inhale hazardous smoke²⁸. However, an independent review of industry documents showed that during initiation and adaption of new smokers, supplemented menthol inhibits physiological warning and rejection responses, thus facilitating easier and continued inhalation despite the harshness of smoke and irritating qualities of nicotine²⁷. This is consistent with the preferential use of mentholated cigarettes by adolescents and young adults who have smoked for less than one year^{29,30}. Thus, the inhalation facilitating effect of menthol is of particular concern for new smokers.

Addictiveness

Many independent studies also demonstrated that

menthol enhances tobacco and nicotine dependence³¹. For example, menthol plus nicotine produced greater reward-related behavior than nicotine alone in a conditioned place preference assay³². Moreover, Wang et al.³³ summarized that: ‘menthol, likely by inducing a cooling sensation, becomes a potent conditioned reinforcer when it is contingently delivered with nicotine’. Importantly, enhanced self-administration of nicotine in response to menthol was linked to TRPM8 activation, as this effect was also induced by an agonist lacking the typical peppermint-like taste. The study by Wang et al.³³ points to an interplay between TRPM8 activation and nicotine dependence, although further work is required to clarify the mechanisms. Furthermore, menthol was demonstrated to sustain nicotine seeking behavior in rats, although this depended on the cooling effect³⁴. Moreover, Biswas et al.³⁵ concluded that menthol directly facilitates nicotine consumption by enhancing its reinforcing effects, thereby contributing to tobacco smoking. In addition, menthol was discussed to inhibit the metabolism of nicotine³⁶, thus facilitating a higher systemic exposure. A recent study demonstrated that menthol increases nicotine-induced dopamine release in the nucleus accumbens of rats³⁷. This may indicate a cumulative rewarding effect of menthol and nicotine. However, another study showed that menthol did not change dopamine release or nicotine self-administration, but did reverse oral nicotine taste aversion in a two-bottle choice test³⁸. Besides, Nesil et al.³⁹ concluded from a study in rats that ‘pharmacological interactions of menthol with nicotine reduce, rather than increase, nicotine’s reinforcing effects and some measures of relapse vulnerability’.

Altogether, a large body of independent literature, except for Nesil et al.³⁹, supports an intricate interaction between nicotine and menthol, which increases the addictiveness and/or attractiveness of tobacco. This seems consistent with the conclusions by the FDA TPSAC in the comprehensive 2011 report on menthol⁴⁰, stating that there is sufficient evidence to indicate that those who smoke menthol-containing products tend to be more dependent. Moreover, menthol has been acknowledged as an additive that can enhance nicotine dependence by a WHO/FCTC expert group consulting on measures to reduce addictiveness of tobacco products⁴¹.

Industry assessment

In contrast to these findings, the industry concluded

that the application of menthol and geraniol does not result in significant effects regarding inhalation facilitation or addictiveness. Importantly, their ability to facilitate inhalation via activation of the TRPM8 receptor was not addressed. The issue whether menthol and geraniol can increase the addictive effects of nicotine was neither comprehensively, nor appropriately covered by the industry reports. The industry provided a pharmacokinetics study aimed to measure smoking parameters and nicotine uptake by established smokers, in which no effects of menthol or geraniol on nicotine uptake were found. In contrast to substantial independent data, the industry’s clinical study on facilitation of inhalation and nicotine uptake has little, if any, relevance to address the crucial role of menthol to promote inhalation during smoking initiation, as all subjects had a smoking history of at least three years and a mean smoking history of 16 years. Since these subjects are already accustomed to the harshness of cigarette smoke, the inhalation facilitating effect of menthol is likely to be less pronounced.

The industry concluded that the clinical study gave no circumstantial indications of increased addictiveness. However, this study was designed to assess inhalation facilitation and nicotine uptake and is therefore not suitable to draw conclusions regarding addictiveness¹⁰. In fact, the industry claims that no valid methods exist to demonstrate a direct effect of a tobacco additive on the addictiveness of the final tobacco product⁷. Thus, they argue that it would be impossible to determine whether any additive affects addictiveness to a relevant degree as required by TPD Article 7, even though there is ample relevant evidence from independent sources for addictive effects of menthol, as described above.

Conclusion and further concerns

There is strong evidence from independent literature that menthol facilitates inhalation by activating the cooling receptor TRPM8. Menthol analogs, including geraniol, have the same agonistic effect on this receptor and can work cumulatively. In addition, independent studies have shown that menthol can enhance the addictive effect of nicotine through various mechanisms and international authorities have acknowledged this effect. Therefore, it can also be concluded that menthol contributes to addictiveness.

In addition, betamyrcene, a pyrolysis product of geraniol, is classified as potentially carcinogenic (Carc. 2B by IARC) but was not assessed in comparative analysis of mainstream smoke. Further, the capacity of menthol and geraniol to facilitate inhalation could lead to increased inhalation of toxicants, which was not considered in the toxicological evaluation.

Sorbitol and guar gum

Sorbitol is a sugar alcohol widely used as an emulsifier, sugar substitute or humectant in food, cosmetics, and healthcare products. It is also added as a humectant to cigarettes and RYO tobacco products¹¹. Guar gum is an extract of the seeds of the guar bean plant. Guar gum consists of high molecular weight polysaccharides and some amount of protein. It is widely used in food as a stabilizer or to improve texture, consistency, softness or other product properties. Guar gum is added as a binder to reconstituted tobacco in cigarettes and is also used to prepare the cigarette paper¹¹.

Main concern: formation of carbonyl compounds

Combustion of sorbitol and guar gum produces carbonyls⁴², some of which have CMR properties and/or potentiate addictive effects of nicotine through the mechanism of MAO inhibition^{43,44}. In the chemical analysis of mainstream smoke in the industry reports, the application of sorbitol and guar gum in test cigarettes caused an additive-level related increase of carbonyl compounds. The industry acknowledged a significant increase in the levels of formaldehyde for both sorbitol and guar gum and acrolein for sorbitol. We also observed a possible rise in other carbonyls that was not acknowledged as significant by the industry. However, we could not conclude regarding significance due to the high variability of the data, most likely due to inconsistencies in the laboratory procedures¹⁰.

As formaldehyde (Carc.1A) and acrolein (IARC 2A) are classified as carcinogens, and formaldehyde is additionally classified as a mutagen (Muta. 2), we conclude that the addition of sorbitol and guar gum contributes to the formation of compounds with CMR properties in mainstream smoke. As some aldehydes also contribute to MAO inhibition, these findings also raise concerns regarding addictiveness. However, neither the increase in CMR compounds nor the potential addictiveness enhancing effect was

addressed in the industry reports.

Further concerns raised

In the smoke chemistry analysis provided by the industry, a statistically significant increase of cadmium (Carc. 1B, Muta 2, Repr 2.) was observed after the addition of sorbitol. This difference in cadmium levels in mainstream smoke (MSS) was not considered by the industry as significant and meaningful since the increase was just below their benchmark requirement (99% variability of 3R4F reference cigarette). We question the validity of this evaluation, as the statistical approach chosen by the industry increased the chance of false-negative results¹⁰.

Although no new pyrolysis experiments were performed, some of the listed pyrolysis products of sorbitol (furfural, Carc. 2; furfuryl alcohol, Carc. 2) and guar gum (furfural, Carc. 2; benzene, Carc. 1A, Muta 1B; toluene, Repr 2; 2-butenal, Muta 2) also have CMR properties. These classified carcinogens were not included in the comparative chemical experiments. Thus, given the application levels of up to 1.2% and 1%, respectively, and the presented data, we conclude that the use of sorbitol and guar gum as additives in cigarettes and RYO tobacco is associated with concern with regard to toxicity.

The industry report has not addressed the impact of sorbitol and guar gum on tobacco flavor or attractiveness. However, pyrolysis of these additives is known to cause the formation of flavoring compounds, which may improve smoke flavor and thereby increase the attractiveness of tobacco products (see also Attractiveness section below). Further, acidic pyrolysis products of guar gum might decrease the smoke pH, possibly making inhalation more palatable⁴².

Carob bean, cocoa, fenugreek, fig, guaiacol, licorice, and maltol

Carob bean, cocoa, fenugreek, fig and licorice are botanicals. They are non-volatile complex mixtures that are added as extract or powder to tobacco and undergo pyrolysis. Guaiacol and maltol are natural compounds that are more or less volatile and mostly stay intact during pyrolysis. All these additives are mainly added as flavorings (see Attractiveness), casings or smoothing agents, while carob bean is also used as a thickener and stabilizer.

Concerns raised

Furfural, which was identified as a pyrolysis product of carob bean, cocoa, fenugreek, fig, licorice and also guar gum and sorbitol, is classified as CMR (Carc. 2) under the EC Regulation No 1272/2008. Furfuryl alcohol, reported as a pyrolysis product of cocoa, licorice, and sorbitol is classified as CMR (Carc. 2) as well. For fenugreek, other pyrolysis products with CMR classifications were benzene (Muta. 1b), toluene (Repr. 2), and crotonaldehyde (Muta. 2). Diacetyl and phenol are pyrolysis products of licorice and have respiratory toxicity (see diacetyl section below) and CMR properties (Muta. 2), respectively. Further, pyrolysis products of carob bean, cocoa, fenugreek, fig, and licorice, mainly aldehydes, may contribute to MAO inhibition. In the comparative chemical assessment reported by the industry, the concentrations of tested aldehydes were not elevated. However, there were methodological limitations in this assessment¹⁰.

In the smoke chemistry analysis provided by the industry, a statistically significant increase of cadmium (Carc. 1B, Muta 2, Repr.) was observed after the addition of cocoa and licorice. These increases were not acknowledged as significant and meaningful by the industry (below benchmark requirement, see Bolling et al.¹⁰). Still, in our opinion, the increase in cadmium is of concern as it may contribute to increased CMR properties of MSS. The level of cadmium was also significantly increased after the addition of guar gum, propylene glycol and sorbitol, but this was only acknowledged by the industry for guar gum (Table 1).

Some of the mentioned additives might have the potential to facilitate inhalation through several different mechanisms. For instance, the industry report indicates that pyrolysis of carob bean, cocoa, fig, licorice and guar gum leads to the formation of acids. Therefore, these additives potentially decrease smoke pH and thereby reduce the harshness of smoke and subsequently facilitate inhalation⁴². Nothing is mentioned about a potential decrease of smoke pH by additives in the industry report. Moreover, previously identified concerns regarding anesthetic effects of guaiaicol that may facilitate inhalation³ have not been addressed by the industry and thus cannot be ruled out. Potential local impacts of theobromine and caffeine from cocoa, e.g. bronchodilatation, have not been assessed nor

discussed either.

As the application levels of the additives vary broadly, the abovementioned concerns must be considered in light of the application level and exposure.

Propylene glycol and glycerol

Propylene glycol and glycerol are non-volatile humectants that transfer mostly intact into MSS¹¹. Humectants are applied in cigarettes to maintain the humidity level of the tobacco during transportation and storage and thus extend the shelf-life of tobacco products. A loss of humidity has been reported to change cigarette smoke composition resulting in an increase of several toxic compounds in MSS accompanied by a harsh and unpleasant perception by the consumer⁴⁵.

Unclear influence on smoke chemistry

Humectants such as glycerol and propylene glycol are considered technically necessary in cigarettes, and it is unlikely that cigarettes without humectants will be commercially available. They greatly influence combustion conditions and consequently the emissions of a range of compounds^{46,47}. The influence of humectants on smoke chemistry was also shown in the comparative experiments performed by the industry, as several compounds were statistically significantly changed in relation to the applied levels of glycerol and propylene glycol.

Test cigarettes containing glycerol and propylene glycol were compared to additive-free control cigarettes that did not contain any humectants in the industry assessment. However, the role of the humectants on the combustion process is not discussed and not adequately assessed to clarify the influence on smoke chemistry. A more detailed discussion of the methodological concerns associated with this approach is provided in Bolling et al.¹⁰.

Titanium dioxide

Titanium dioxide (TiO₂) is used as a whitening agent in cigarette filters, where it is bound to the filter material. It has also been reported as an ingredient of filter paper inks, tipping paper and tipping inks¹¹. The European Commission has classified TiO₂ as a carcinogen (Carc. 2) by inhalation, the classification became effective on 9 September 2021⁴⁸. This

classification applies to mixtures in powder form containing 1% or more of TiO_2 in the form of, or incorporated in, particles with an aerodynamic diameter $\leq 10 \mu\text{m}$. In EU-CEG, there is currently no information regarding the size of particles of TiO_2 applied in cigarettes provided by tobacco manufacturers.

The industry performed a transfer study to determine whether TiO_2 is released in MSS to assess consumer exposure. In this study, puffs were drawn from unlit cigarettes to monitor whether particles were carried over into the airstream. Under the applied experimental conditions, few TiO_2 particles were identified, one with a size below $10 \mu\text{m}$. The industry concluded that applied levels of TiO_2 did not increase CMR properties during consumption. However, they had used optical light microscopy in these tests, which is not suitable to detect the possible presence of nanoparticles. Instead, transmission electron microscopy is required for the detection of nano-sized particles. Moreover, in the applied experimental approach, the potential influence of mechanical stress (i.e. the smokers' handling of the filter) during consumption and the composition and temperature of MSS on the transfer of TiO_2 were neglected. Overall, the experimental set-up was not sufficiently sensitive to detect nano-sized particles and not relevant to the real-world situation where cigarettes are lit and hand-held. In addition, possible side-effects of TiO_2 , such as catalyst properties on pyrolysis and the subsequent impact on smoke chemistry, were not addressed. Further, assessment of addictiveness, inhalation facilitation and characterizing flavor, despite being required by the TPD, were not provided

Due to the limitations in the industry's assessment of TiO_2 , we conclude that the data presented by the industry are not sufficient to demonstrate the absence of titanium dioxide particles in their nano form in MSS. Consequently, the concern regarding carcinogenicity due to particulate titanium dioxide in MSS has not been ruled out. Further, the TPD prohibits placing tobacco products containing additives that have CMR properties in unburnt form on the market. Thus, products containing or producing TiO_2 particles with an aerodynamic diameter $\leq 10 \mu\text{m}$ that may be inhaled do not comply with the TPD.

Diacetyl

The industry provided no report for diacetyl. The four lead companies initially forming the industry consortium have stated that diacetyl is not added to their cigarettes or RYO tobacco⁷. Since the industry provided no report, we performed a non-comprehensive literature review for diacetyl⁹.

In some types of tobacco, diacetyl is naturally present, but it may also be added as a flavoring to the tobacco product. However, the major amount of diacetyl in cigarette smoke is formed during the pyrolysis of constituents such as sugars, including sucrose and glucose^{42,49,50}.

Inhalation toxicity

Numerous lines of evidence suggest that exposure to high concentrations of diacetyl causes long-term impairments in pulmonary function. In various in vivo experimental studies, diacetyl has been reported to cause injury to the nasal, tracheal and bronchial epithelium⁵¹⁻⁵³.

Kreiss et al.⁵⁴ noted the development of respiratory symptoms in popcorn factory workers (exposed to diacetyl), including evidence of airway obstruction. The clinical effects of diacetyl on the human respiratory tract include cough, shortness of breath and wheezing. In addition, histological and morphological changes in the lung have been observed that are consistent with bronchiolitis obliterans (BO), a fibrotic lung disease with obstructions in the small airways⁵⁵⁻⁵⁹.

The United States National Institute for Occupational Safety and Health (NIOSH) estimated an average exposure to diacetyl of 0.45 to 1.3 ppm diacetyl per cigarette. The 8-hour time-weighted average equivalent of a smoker who smokes 20 cigarettes per day was 0.17 to 0.50 ppm⁴³. The link between diacetyl and the generation of BO has been challenged in some publications, as reviewed by the European Scientific Committee on Occupational Exposure Levels (SCOEL). Nevertheless, SCOEL concluded that the evidence is sufficient to suggest that diacetyl can cause mild to life-threatening airway obstruction. SCOEL and NIOSH suggested 8-hour time-weighted average occupational exposure limits of 0.02 ppm and 0.005 ppm, respectively. These levels are exceeded by cigarette smoking. NIOSH also hypothesized that diacetyl

might contribute to the development of Chronic Obstructive Pulmonary Disease (COPD) in smokers. Although the primary source of diacetyl in MSS is pyrolysis^{42,49,50}, application of diacetyl as an additive may also contribute to increased diacetyl levels in MSS.

Further concern raised

The Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) raised concerns regarding uncertainties about genotoxicity and unknown carcinogenicity of diacetyl^{3,11}.

Attractiveness of additives

Many of the additives on the priority additive list and their pyrolysis products are known flavorings and/or sweeteners (including carob bean, cocoa, fenugreek, fig, guaiacol and licorice, but also diacetyl, geraniol, guar gum, menthol and sorbitol)¹¹. These substances modify the flavor of cigarettes, making them more attractive, especially for young and new users. Moreover, some additives increase the palatability of cigarettes due to their humidifying properties (including sorbitol, propylene glycol, and glycerol). The addition of flavorings and humectants making the cigarette attractive and palatable is in itself cause for concern. Additives that increase the attractiveness of tobacco products ultimately increase the risk for addiction and tobacco-related harm by promoting smoking initiation and maintenance and increasing consumption rates^{60,61}.

The TPD recognizes the concern of attractiveness of tobacco products in the introduction and Article 19.1 (a)¹. However, attractive properties other than characterizing flavors are currently not regulated, and their assessment is not required and consequently not provided by the tobacco industry. The industry only provided a sensory analysis for carob bean, cocoa, fenugreek, fig, geraniol, guaiacol, licorice and menthol, to assess whether these additives lead to a characterizing flavor. According to that assessment, none of the additives besides menthol provided a characterizing flavor to cigarettes at tested levels. However, we question the validity of this conclusion due to methodological limitations in the assessment¹⁰. Significantly,

even in the absence of characterizing flavors, priority additives may increase the palatability and attractiveness of cigarettes and RYO tobacco by modifying the perceived flavor, taste or odor, or by their humectant properties.

DISCUSSION

Overall, the industry reports have an unclear structure, which significantly hindered the scientific evaluation of the provided studies. Moreover, the reports are not comprehensive, mostly due to limitations in the overall approach chosen and a range of specific methodological limitations, summarized in Bolling et al.¹⁰. As a consequence of the poor quality of the reports, we question the scientific validity of the conclusions in the industry reports and conclude that these are not warranted. Therefore, we conclude that the industry did not sufficiently fulfil the reporting obligations in the TPD.

The weaknesses and deficiencies in the provided reports demonstrate that the tobacco industry cannot be considered an unbiased party in assessing their own products. The lack of inclusion of solid evidence from independent literature on menthol's capacity to facilitate inhalation and enhance addictiveness is one clear example of such bias. This exclusion points towards a deliberate decision from the industry consortium to ignore existing evidence. Therefore, we recommend that information from the tobacco industry should not be used as the sole basis for the regulation of tobacco products.

The industry concluded that none of the additives is associated with concern when used in cigarettes or RYO tobacco. In contrast, our review demonstrates that many issues regarding toxicity and addictiveness of the additives have not been sufficiently addressed, and therefore concerns remain for a range of additives.

For menthol, a ban on cigarettes and RYO products containing a concentration that leads to a characterizing flavor based on the TPD (Art 7.1) is already enforced. In addition, we found strong evidence in independent literature confirming that menthol facilitates inhalation by activating the cooling receptor TRPM8. This facilitation of inhalation is an intrinsic property of menthol (and its analogs) and can occur at levels far below the threshold of characterizing flavor. Menthol analogs,

including geraniol, have the same agonistic effect on this receptor and may work cumulatively. According to Article 7.6 of the TPD, tobacco products for smoking containing additives that facilitate inhalation or nicotine uptake shall not be placed on the market. Therefore, we conclude that the addition of menthol and geraniol (and other activators of the TRPM8 receptor) in any application level is not in compliance with the TPD. Finland and Germany already enforce a ban on menthol (and several of its analogs in the case of Germany⁶²) at any application level, based on their inhalation facilitating properties⁶³.

Menthol also contributes to addictiveness via various mechanisms. However, since there are currently no validated tests to demonstrate (or disprove) a significant or measurable increase of addictiveness due to a change in one additive at the stage of consumption, regulation of menthol based on its contribution to addictiveness is hampered by the current phrasing of paragraphs 6.2 and 7.9 of the TPD.

Sorbitol and guar gum were found to increase the formation of some carbonyl compounds with CMR properties to a measurable and significant degree. In addition, increased aldehyde levels may contribute to addictiveness through MAO inhibition. This effect has been previously demonstrated for combustion products of added sugars. The potentiation of addictive effects of nicotine through the mechanism of MAO inhibition^{43,44} was also indicated in the 2010 SCENIHR report and acknowledged at the WHO workshop on addictiveness in 2018 (WHO, Berlin, Germany 15–16 May 2018)^{41,64}. However, regulation of sugars and similar tobacco additives may be easily circumvented, as other unregulated compounds, including complex carbohydrates or sugar alcohols, might be added as substitutes for sugars, resulting in the same effect. As suggested by the WHO Study Group on tobacco product regulation (TobReg), a more promising approach would be to set limits for the yields of aldehydes (and other toxicants) per cigarette⁶⁵. Pennings et al.⁶⁶ demonstrated that formaldehyde yields are beneficial to monitor emissions of other toxicants, including carbonyls. Therefore, we advise the EC and MS to consider whether mandatory limits for selected aldehydes in MSS are suitable measures to restrict the effects of

sugars and related additives on tobacco products' toxicity and addictiveness⁶⁵.

Titanium dioxide in particles with an aerodynamic diameter $\leq 10 \mu\text{m}$ is classified as a carcinogen (Carc. 2) by inhalation. As TPD Article 7 states that tobacco products containing additives with CMR properties shall not be placed on the market¹, such particles should not be included in tobacco products if they are inhaled. The experiment provided in the industry report does not demonstrate the absence of titanium dioxide particles in MSS, and thus concerns regarding carcinogenicity cannot be ruled out. To enforce a ban based on the classification, MS might request information from the industry about the particle size of the titanium dioxide used and representative experiments that demonstrate whether or not these particles are present in MSS.

For diacetyl, no industry report was provided, and thus the reporting obligations in the TPD were not met. Diacetyl can cause mild to life-threatening airway obstruction and is likely to contribute to tobacco toxicity. Given that the primary source of diacetyl in MSS is pyrolysis, potential regulation of diacetyl as an additive may be complemented or replaced by regulation of additives that promote diacetyl generation. Although diacetyl is rarely added to cigarettes anymore, it is still frequently used in other tobacco products (based on Dutch EU-CEG data retrieved in 2021) and e-liquids⁶⁷. We, therefore, recommend that the effects of the application of diacetyl in these products should be carefully evaluated. The addition of diacetyl to e-liquids is prohibited in Germany due to its inhalation toxicity⁵⁶.

Many of the priority list additives and their pyrolysis products are flavorings, sweeteners and humectants that increase the palatability and attractiveness of cigarettes and other tobacco products. This is concerning as this may facilitate smoking initiation, particularly among adolescents. Properties that increase the attractiveness of a product (other than characterizing flavor) are currently not regulated by the TPD and consequently not assessed by the industry. Considering the raised concerns, we recommend that regulation of attractive product properties should be incorporated in future versions of the TPD. Until then, MS are advised to explore other regulatory options to limit the

attractiveness of tobacco products.

CONCLUSION

Although restricting the use of priority additives may contribute to improved public health, enforcement of product bans based on several of these concerns is complicated due to the specific type of evidence required by the current phrasing of the TPD. We therefore strongly recommend a revision of paragraphs 6.2 and 7.9 of the TPD, both to ensure unambiguous interpretation and effective regulation of tobacco products and their ingredients. Moreover, the procedure itself (i.e. composing a list of priority additives, requiring tobacco manufacturers to provide data regarding their effects – without specifications or guidelines – and the independent scientific review of the industry reports) has been highly resource-intensive and delivered little actionable information. The data presented in the industry reports provide an insufficient basis for the regulation of most additives. Ideally, a comprehensive and systematic literature review should be performed by an independent body to obtain unbiased evidence regarding the effects of the priority additives. Furthermore, alternative regulatory approaches should be considered, such as setting limits to the yields of toxicants per cigarette, as suggested by the WHO Study Group on tobacco product regulation (TobReg)⁶⁵.

Moreover, MS may consider applying the precautionary principle⁶⁸ by banning additives for which concerns regarding their application in tobacco products have not been ruled out. Ultimately, each MS must consider whether the currently presented concerns regarding priority additives are sufficient to implement national bans on tobacco additives.

REFERENCES

1. DIRECTIVE 2014/40/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC. Official Journal of the European Union; 2014. April 29, 2014. Accessed June 21, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014L0040&from=EN>
2. 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 (notified under document C(2016) 2923). Official Journal of the European Union; 2016. May 20, 2016. Accessed June 21, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016D0787&from=EN>
3. Final Opinion on Additives used in tobacco products (Opinion 1), Tobacco Additives I. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); 2016. January 25, 2016. Accessed June 21, 2022. https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_051.pdf
4. Hoet P, Rydzynski K, Vermeire T, et al. Recommendations to the European Commission implementing a priority list of additives that should have more stringent reporting requirements: the opinion of the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR). *Tob Control*. 2018;27(2):225-228. doi:10.1136/tobaccocontrol-2017-053642
5. Carnicer-Pont D, Tigova O, Havermans A, et al. Tobacco products in the European Union Common Entry Gate (EU-CEG): A tool for monitoring the EU tobacco products directive. *Tob Prev Cessat*. 2022;8(March):1-11. doi:10.18332/tpc/145501
6. McEwan M, Coburn S, Ghosh D, et al. Assessment of priority tobacco additives per the requirements of the EU Tobacco Products Directive (2014/40/EU): Part 3, Smoking behavior and plasma nicotine pharmacokinetics. *Regul Toxicol Pharmacol*. 2019;104:29-38. doi:10.1016/j.yrtp.2019.02.012
7. Simms L, Clarke A, Paschke T, et al. Assessment of priority tobacco additives per the requirements of the EU Tobacco Products Directive (2014/40/EU): Part 1: Background, approach, and summary of findings. *Regul Toxicol Pharmacol*. 2019;104:84-97. doi:10.1016/j.yrtp.2019.02.011
8. Stabbert R, Ghosh D, Clarke A, et al. Assessment of priority tobacco additives per the requirements in the EU Tobacco Products Directive (2014/40/EU): Part 2: Smoke chemistry and in vitro toxicology. *Regul Toxicol Pharmacol*. 2019;104:163-199. doi:10.1016/j.yrtp.2019.03.002
9. National Institute for Public Health and the Environment, German Federal Institute for Risk Assessment, Berlin, Germany, French Agency for Food, Environmental and Occupational Health and Safety, Norwegian Institute of Public Health, Istituto Superiore di Sanità, WP9 Independent Review Panel. Agreement n° 761297-JATC-HP-JA-03-2016: WP9-D9.3 Report on the peer review of the enhanced reporting information on priority additives. European Union; 2020. December 3, 2020. Accessed June 21, 2022. <https://jaotc.eu/wp-content/uploads/2021/04/D9.3-Report-on-the-peer-review-of-the-enhanced-reporting-information-on-priority-additives.pdf>

10. Bolling AK, Mallock N, Zervas E, et al. Review of industry reports on EU priority tobacco additives Part B: Methodological limitations. *Tob Prev Cessation*. 2022;8(July):1-16. doi:10.18332/tpc/150361
11. Opinion on Additives used in tobacco products (Opinion 2), Tobacco Additives II. Scientific Committee on Health, Environmental and Emerging Risks (SCHEER); 2016. December 16, 2016. Accessed June 21, 2022. https://ec.europa.eu/health/system/files/2017-02/scheer_o_001_0.pdf
12. Talhout R, Duarte-Davidson R, Hoet P, et al. Advice to the European Commission as Regards Type and Criteria for Comprehensive Studies to Be Requested From Manufacturers: The Opinion of the Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER). *Nicotine Tob Res*. 2020;22(5):613-618. doi:10.1093/ntr/ntz006
13. Mączka W, Wińska K, Grabarczyk M. One Hundred Faces of Geraniol. *Molecules*. 2020;25(14):3303. doi:10.3390/molecules25143303
14. Kreslake JM, Wayne GF, Alpert HR, Koh HK, Connolly GN. Tobacco industry control of menthol in cigarettes and targeting of adolescents and young adults. *Am J Public Health*. 2008;98(9):1685-1692. doi:10.2105/AJPH.2007.125542
15. Ha MA, Smith GJ, Cichocki JA, et al. Menthol attenuates respiratory irritation and elevates blood cotinine in cigarette smoke exposed mice. *PLoS One*. 2015;10(2):e0117128. doi:10.1371/journal.pone.0117128
16. Dunér-Engström M, Larsson O, Lundberg J, Fredholm BB. Effect of nicotine chewing gum on salivary secretion. *Swed Dent J*. 1986;10(3):93-96.
17. Squier CA, Mantz MJ, Wertz PW. Effect of menthol on the penetration of tobacco carcinogens and nicotine across porcine oral mucosa ex vivo. *Nicotine Tob Res*. 2010;12(7):763-767. doi:10.1093/ntr/ntq084
18. Dicipinigaitis PV, Morice AH, Birring SS, et al. Antitussive drugs--past, present, and future. *Pharmacol Rev*. 2014;66(2):468-512. doi:10.1124/pr.111.005116
19. Eccles R. Menthol and related cooling compounds. *J Pharm Pharmacol*. 1994;46(8):618-630. doi:10.1111/j.2042-7158.1994.tb03871.x
20. Willis DN, Liu B, Ha MA, Jordt SE, Morris JB. Menthol attenuates respiratory irritation responses to multiple cigarette smoke irritants. *FASEB J*. 2011;25(12):4434-4444. doi:10.1096/fj.11-188383.
21. Laude EA, Morice AH, Grattan TJ. The antitussive effects of menthol, camphor and cineole in conscious guinea-pigs. *Pulm Pharmacol*. 1994;7(3):179-184. doi:10.1006/pulp.1994.1021
22. Millqvist E, Ternesten-Hasséus E, Bende M. Inhalation of menthol reduces capsaicin cough sensitivity and influences inspiratory flows in chronic cough. *Respir Med*. 2013;107(3):433-438. doi:10.1016/j.rmed.2012.11.017
23. Behrendt HJ, Germann T, Gillen C, Hatt H, Jostock R. Characterization of the mouse cold-menthol receptor TRPM8 and vanilloid receptor type-1 VR1 using a fluorometric imaging plate reader (FLIPR) assay. *Br J Pharmacol*. 2004;141(4):737-745. doi:10.1038/sj.bjp.0705652
24. Jiang K, Zhang T, Yin N, et al. Geraniol alleviates LPS-induced acute lung injury in mice via inhibiting inflammation and apoptosis. *Oncotarget*. 2017;8(41):71038-71053. doi:10.18632/oncotarget.20298
25. Xue Z, Zhang XG, Wu J, et al. Effect of treatment with geraniol on ovalbumin-induced allergic asthma in mice. *Ann Allergy Asthma Immunol*. 2016;116(6):506-513. doi:10.1016/j.anaai.2016.03.029
26. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. *Nature*. 2002;416(6876):52-58. doi:10.1038/nature719
27. Yerger VB, McCandless PM. Menthol sensory qualities and smoking topography: a review of tobacco industry documents. *Tob Control*. 2011;20(Suppl_2):ii37-ii43. doi:10.1136/tc.2010.041988
28. Strasser AA, Ashare RL, Kaufman M, Tang KZ, Mesaros AC, Blair IA. The effect of menthol on cigarette smoking behaviors, biomarkers and subjective responses. *Cancer Epidemiol Biomarkers Prev*. 2013;22(3):382-389. doi:10.1158/1055-9965.EPI-12-1097
29. Rising J, Wasson-Blader K. Menthol and initiation of cigarette smoking. *Tob Induc Dis*. 2011;9(Suppl 1):S4. doi:10.1186/1617-9625-9-S1-S4
30. Hersey JC, Ng SW, Nonnemaker JM, et al. Are menthol cigarettes a starter product for youth? *Nicotine Tob Res*. 2006;8(3):403-413. doi:10.1080/14622200600670389
31. Wickham RJ. The Biological Impact of Menthol on Tobacco Dependence. *Nicotine Tob Res*. 2020;22(10):1676-1684. doi:10.1093/ntr/ntz239
32. Henderson BJ, Wall TR, Henley BM, Kim CH, McKinney S, Lester HA. Menthol Enhances Nicotine Reward-Related Behavior by Potentiating Nicotine-Induced Changes in nAChR Function, nAChR Upregulation, and DA Neuron Excitability. *Neuropsychopharmacology*. 2017;42(12):2285-2291. doi:10.1038/npp.2017.72
33. Wang T, Wang B, Chen H. Menthol facilitates the intravenous self-administration of nicotine in rats. *Front Behav Neurosci*. 2014;8:437. doi:10.3389/fnbeh.2014.00437
34. Harrison E, Biswas L, Avusula R, Zhang M, Gong Y, Liu X. Effects of menthol and its interaction with nicotine-conditioned cue on nicotine-seeking behavior in rats. *Psychopharmacology (Berl)*. 2017;234(23-24):3443-3453. doi:10.1007/s00213-017-4736-0
35. Biswas L, Harrison E, Gong Y, et al. Enhancing effect of menthol on nicotine self-administration in rats. *Psychopharmacology (Berl)*. 2016;233(18):3417-3427. doi:10.1007/s00213-016-4391-x
36. Benowitz NL, Herrera B, Jacob P. Mentholated cigarette smoking inhibits nicotine metabolism. *J Pharmacol Exp Ther*. 2004;310(3):1208-1215.

- doi:10.1124/jpet.104.066902
37. Zhang M, Harrison E, Biswas L, Tran T, Liu X. Menthol facilitates dopamine-releasing effect of nicotine in rat nucleus accumbens. *Pharmacol Biochem Behav.* 2018;175:47-52. doi:10.1016/j.pbb.2018.09.004
 38. Wickham RJ, Nunes EJ, Hughley S, et al. Evaluating oral flavorant effects on nicotine self-administration behavior and phasic dopamine signaling. *Neuropharmacology.* 2018;128:33-42. doi:10.1016/j.neuropharm.2017.09.029
 39. Nesil T, Narmeen S, Bakhti-Suroosh A, Lynch WJ. Effect of menthol on nicotine intake and relapse vulnerability in a rat model of concurrent intravenous menthol/nicotine self-administration. *Psychopharmacology (Berl).* 2019;236(4):1219-1232. doi:10.1007/s00213-018-5128-9
 40. PRELIMINARY SCIENTIFIC EVALUATION OF THE POSSIBLE PUBLIC HEALTH EFFECTS OF MENTHOL VERSUS NONMENTHOL CIGARETTES. Food and Drug Administration; 2013. Accessed June 21, 2022. <https://www.fda.gov/media/86497/download>
 41. Report: consultation on tobacco addictiveness reduction measures, Berlin, Germany, 15-16 May 2018. World Health Organization; 2018. Accessed June 21, 2022. <https://apps.who.int/iris/rest/bitstreams/1153681/retrieve>
 42. Talhout R, Opperhuizen A, van Amsterdam JG. Sugars as tobacco ingredient: Effects on mainstream smoke composition. *Food Chem Toxicol.* 2006;44(11):1789-1798. doi:10.1016/j.fct.2006.06.016
 43. Guillem K, Vouillac C, Azar MR, et al. Monoamine oxidase A rather than monoamine oxidase B inhibition increases nicotine reinforcement in rats. *Eur J Neurosci.* 2006;24(12):3532-3540. doi:10.1111/j.1460-9568.2006.05217.x
 44. Villégier AS, Salomon L, Granon S, et al. Monoamine oxidase inhibitors allow locomotor and rewarding responses to nicotine. *Neuropsychopharmacology.* 2006;31(8):1704-11713. doi:10.1038/sj.npp.1300987
 45. Rodgman A. Some Studies of the Effects of Additives on Cigarette Mainstream Smoke Properties. II. Casing Materials and Humectants. *Beitr Tab Int.* 2002;20(4):279-299. doi:10.2478/cttr-2013-0742
 46. Rodgman A. Some Studies of the Effects of Additives on Cigarette Mainstream Smoke Properties. I. Flavorants. *Beitr Tab Int.* 2002;20(2):83-103. doi:10.2478/cttr-2013-0734
 47. Baker RR, Pereira da Silva JR, Smith G. The effect of tobacco ingredients on smoke chemistry. Part II: casing ingredients. *Food Chem Toxicol.* 2004;42:S39-S52. doi:10.1016/j.fct.2003.08.009
 48. COMMISSION DELEGATED REGULATION (EU) 2020/217 of 4 October 2019 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures and correcting that Regulation. Official Journal of the European Union; 2020. February 18, 2020. Accessed June 21, 2022. <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32020R0217&from=EN>
 49. Pierce JS, Abelmann A, Spicer LJ, Adams RE, Finley BL. Diacetyl and 2,3-pentanedione exposures associated with cigarette smoking: implications for risk assessment of food and flavoring workers. *Crit Rev Toxicol.* 2014;44(5):420-435. doi:10.3109/10408444.2014.882292
 50. Roemer E, Schorp MK, Piadé JJ, Seeman JI, Leyden DE, Haussmann HJ. Scientific assessment of the use of sugars as cigarette tobacco ingredients: a review of published and other publicly available studies. *Crit Rev Toxicol.* 2012;42(3):244-278. doi:10.3109/10408444.2011.650789
 51. Hubbs AF, Battelli LA, Goldsmith WT, et al. Necrosis of nasal and airway epithelium in rats inhaling vapors of artificial butter flavoring. *Toxicol Appl Pharmacol.* 2002;185(2):128-135. doi:10.1006/taap.2002.9525
 52. Hubbs AF, Goldsmith WT, Kashon ML, et al. Respiratory toxicologic pathology of inhaled diacetyl in sprague-dawley rats. *Toxicol Pathol.* 2008;36(2):3303-44. doi:10.1177/0192623307312694
 53. Palmer SM, Flake GP, Kelly FL, et al. Severe airway epithelial injury, aberrant repair and bronchiolitis obliterans develops after diacetyl instillation in rats. *PLoS One.* 2011;6(3):e17644. doi:10.1371/journal.pone.0017644
 54. Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes EJ, Enright PL. Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N Engl J Med.* 2002;347(5):330-338. doi:10.1056/NEJMoa020300
 55. Akpınar-Elci M, Travis WD, Lynch DA, Kreiss K. Bronchiolitis obliterans syndrome in popcorn production plant workers. *Eur Respir J.* 2004;24(2):298-302. doi:10.1183/09031936.04.00013903
 56. Kanwal R, Kullman G, Piacitelli C, et al. Evaluation of flavorings-related lung disease risk at six microwave popcorn plants. *J Occup Environ Med.* 2006;48(2):149-157. doi:10.1097/01.jom.0000194152.48728.fb
 57. Kreiss K. Work-related spirometric restriction in flavoring manufacturing workers. *Am J Ind Med.* 2014;57(2):129-137. doi:10.1002/ajim.22282
 58. Kreiss K, Fedan KB, Nasrullah M, et al. Longitudinal lung function declines among California flavoring manufacturing workers. *Am J Ind Med.* 2012;55(8):657-668. doi:10.1002/ajim.21013
 59. van Rooy FG, Rooyackers JM, Prokop M, Houba R, Smit LA, Heederik DJ. Bronchiolitis obliterans syndrome in chemical workers producing diacetyl for food flavorings. *Am J Respir Crit Care Med.* 2007;176(5):498-504. doi:10.1164/rccm.200611-16200C
 60. Nair U. Additives in Tobacco Products: Contribution of Carob Bean Extract, Cellulose Fibre, Guar Gum, Liquorice, Menthol, Prune Juice Concentrate and Vanillin to Attractiveness, Addictiveness and Toxicity of Tobacco Smoking. German Cancer Research Center; 2012. Accessed June 21, 2022. <https://www.dkfz.de/de/>

- tabakkontrolle/download/PITOC/PITOC_Additives_in_Tobacco_Products_Report.pdf
61. Ferreira CG, Silveira D, Hatsukami DK, et al. The effect of tobacco additives on smoking initiation and maintenance. *Cad Saude Publica*. 2015;31(2):223-225. doi:10.1590/0102-311xpe010215
 62. Verordnung über Tabakerzeugnisse und verwandte Erzeugnisse. Regulation for Tobacco Products and Related Products. Legislation in German. Bundesministeriums der Justiz; 2016. April 27, 2016. Accessed June 21, 2022. <https://www.gesetze-im-internet.de/tabakerzv/TabakerzV.pdf>
 63. Menthol tobacco products and menthol e-cigarette liquids may not be sold in Finland. National Supervisory Authority for Welfare and Health (Valvira); 2020. December 1, 2020. Updated December 2, 2020. Accessed June 21, 2022. <https://www.valvira.fi/web/en/-/menthol-tobacco-products-and-menthol-e-cigarette-liquids-may-not-be-sold-in-finland>
 64. Addictiveness and Attractiveness of Tobacco Additives. Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR); 2010. July 6, 2010. Accessed June 21, 2022. https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_029.pdf
 65. Burns DM, Dybing E, Gray N, et al. Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal. *Tob Control*. 2008;17(2):132-141. doi:10.1136/tc.2007.024158
 66. Pennings JLA, Cremers JWJM, Becker MJA, Klerx WNM, Talhout R. Aldehyde and Volatile Organic Compound Yields in Commercial Cigarette Mainstream Smoke Are Mutually Related and Depend on the Sugar and Humectant Content in Tobacco. *Nicotine Tob Res*. 2020;22(10):1748-1756. doi:10.1093/ntr/ntz203
 67. Eshraghian EA, Al-Delaimy WK. A review of constituents identified in e-cigarette liquids and aerosols. *Tob Prev Cessat*. 2021;7(February):1-15. doi:10.18332/tpc/131111
 68. Bourguignon D. The precautionary principle: Definitions, applications and governance. European Parliamentary Research Service; 2016. doi:10.2861/821468

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CONFLICTS OF INTEREST

The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none was reported.

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ETHICAL APPROVAL AND INFORMED CONSENT

Ethical approval and informed consent were not required for this study.

DATA AVAILABILITY

The data supporting this research are available from the authors on reasonable request.

AUTHORS' CONTRIBUTIONS

AH, AKB, NM, EZ and CL conceptualized the manuscript and wrote the initial draft. All the authors provided comments and suggestions to the manuscript versions and approved the final version.

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