Juul Labs' Consolidated Response to the Preliminary Opinion of the European Commission and its Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) on electronic cigarettes

Juul Labs is committed to working cooperatively with regulators in every market we operate to help adult smokers find alternatives to combustible cigarettes while combating underage use. To further advance the harm reduction potential vapour products have for adult smokers, it is essential that any discussion and decision regarding the vapour category be rooted in science.

As part of Juul Labs' dedication to science and evidenced-based regulation of all tobacco and nicotine-containing products we will periodically submit comments, including scientific evidence, as part of regulatory and policy-making consultations. Recently, the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published a preliminary Opinion on electronic cigarettes. Interested parties were invited to submit comments before October 26, 2020. In our efforts to add to the conversation, Juul Labs submitted comments for review.

Below is a consolidation of our comments and data submitted for the Committee's consideration. Due to the nature of the process, our comments were provided in sections of the SCHEER preliminary Opinion. Therefore, we have consolidated all our comments below to provide a comprehensive representation of our arguments and positions. A full review of our comments can be seen here . The language used in our responses below mirrors the language used by SCHEER.

This information is for policymakers and regulators and is not for advertising or promotional purposes or intended for a consumer audience.

Introduction: Comments regarding EU Mandate, Purpose and Methodology

1. Summary

The Opinion summarises the main purpose of SCHEER's review: "*The Opinion addresses the role of electronic cigarettes, focusing on potential impacts in the EU context, in relation to:*

1. *their use and adverse health effects (i.e.; short- and long-term effects) risks associated with their technical design and chemical composition (e.g.; number and levels of toxicants) and with the existing EU regulatory framework (e.g. nicotine concentration and limits)*
2. *their role as a gateway to smoking / the initiation of smoking (particularly focusing on young people)*
3. *their role in cessation of traditional tobacco smoking*".

The SCHEER Opinion does not utilise data commissioned by the European Commission showing that 61% of respondents polled for the Eurobarometer survey indicate the e-cigarettes are "to stop or reduce tobacco consumption"[1] and that when used as a substitute for cigarettes, they significantly reduce

[1] Special Eurobarometer 458 "Attitudes of Europeans towards tobacco and electronic cigarettes" European Union, 2017 Survey conducted by TNS political & social at the request of the European Commission, Directorate-General

exposure to the harmful toxicants found in tobacco smoke[2]. 26% of EU citizens are smokers. Smokers are at serious risk of disease and premature death – with 700,000 dying each year.[3] This is the population most at risk of avoidable cancer and the population that would most benefit from an effective EU Beating Cancer Plan.

The risk of e-cigarette use must be positioned relative to the well-established risks of continuing smoking. The fundamental information about comparative risk is absent throughout SCHEER's Opinion, yet it is the central public health proposition that e-cigarettes can and do offer. Studies such as Stephens et al. 2018 or George et al., 2019 found, respectively, that e-cigarette users were typically exposed to 0.4% of the lifetime cancer risk of smokers and that evidence of significant improvements in cardiovascular outcomes in smokers who switch to e-cigarettes do exist and are well proven.[4] Such studies need to be thoroughly and fully reviewed by SCHEER in its Opinion.

2. Mandate from the EU Commission Services

At several points the Opinion notes that "*this Opinion is restricted to the terms of references given by the European Commission*". It is therefore important to understand both the letter and the intention of those terms of reference. The terms of reference clearly state that *"the main purpose of the scientific opinion is to assist the Commission in assessing the most recent scientific and technical information on e-cigarettes*." This assessment is part of and will feed into the report that the Tobacco Products Directive (TPD) requires out of the Commission services by 21 May 2021.[5]

The mandate establishes that both the Commission report and the scientific review performed by SCHEER comes directly from the co-legislators volition expressed within TPD, described as "*aim(ing) to improve the functioning of the internal market for tobacco and related products, while ensuring a high level of health protection for European citizens*." *It is also noted that Article 20 of the Tobacco Products Directive "introduces for the first time a comprehensive regulatory framework for electronic cigarettes with a focus on safety, quality, consumer protection and collection of information."*

A joint reading of those two parts would indicate that the primary focus of this Opinion should consist of

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for Health and Food safety (DG SANTE)

[2] For review see, "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/ reports/2018/public-health-consequences-of-e-cigarettes.aspx and McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England. London: Public Health England.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf

[3] "700,000 deaths a year: tackling smoking in the EU," European Parliament News, May 2016.

[4] Stephens WE, Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke
Tobacco Control 2018;**27:**10-17.
George J, Hussain M, Vadiveloo T, et al. Cardiovascular Effects of Switching From Tobacco Cigarettes to Electronic Cigarettes. J Am Coll Cardiol. 2019;74(25):3112-3120.

[5] Directive 2014/40/EU of The European Parliament and of The Council
of 3 April 2014 https://ec.europa.eu/health//sites/health/files/tobacco/docs/dir_201440_en.pdf

1) Evidence regarding e-cigarette products that are TPD compliant and legally available to EU consumers - and their quality and level of consumer protection;[6]

2) Data and studies collected/performed by Member States' regulatory authorities reviewing TPD-compliant e-cigarettes marketed on their territories;[7]

3) The most recently available scientific and technical information including scientific and technical studies performed on EU marketed devices and liquids post 2014;

4) Reviews from other markets (including the United States) as comparison points to EU marketed products when appropriate (as opposed to default).

As detailed in subsequent sections, there are several points in this Opinion where the Committee strays from the intended focus of a review of e-cigarettes compliant with the TPD. First, the Committee's review often refers to device combinations sold in the United States without reference to differences in regulatory schemes preventing their equivalence in the EU (pages 8, 18 and 21). Furthermore, the Committee often relies on outdated scientific and technical information that may no longer be relevant to TPD-compliant e-cigarettes.

Finally, given the general purpose of TPD but also considering the well-documented consumer substitution of combustible tobacco for e-cigarette products, a proper understanding of any potential human health effects of e-cigarettes would have included a proper assessment of not just absolute but risk relative to combustible cigarettes, which e-cigarettes are designed to replace.

4. Methodology

We find the methodology used to synthesise this Opinion problematic for many reasons. We found the following methodological items to be missing, including the search terms and databases used to gather relevant literature, inclusion criteria, quality assessment and justification for inclusion of articles. The Opinion simply states that most information is derived from review articles and that primary sources are used 'if necessary'.

In addition, how assessments, particularly the weighting of evidence (WOE), were made, including providing definitions for the levels of assessment (strong, moderate, weak, uncertain, or not possible), and agreed upon by the Committee was not reported.

Recognising that information from a single piece of evidence is rarely sufficient, WOE refers to an approach that uses a combination of information from several independent sources giving sufficient evidence to fulfil an information requirement. However, in failing to define WOE criteria the reader

[6] These are products marketed within the EU after 20 May 2016 and/or those marketed in EU Member States from the date of their TPD transposition (between 21 May 2014 and 20 May 2016).

[7] Such data and studies, collected and released by independent, reputable and well-respected national regulatory authorities that could have been thoroughly reviewed include reviews listed in footnote 2 (NASEM 2018 and PHE 2020). These reports should be used to the full extent.

needs to have expertise in the relevant topics in order to gain full understanding of the opinion provided by the Committee and ensure accuracy.[8]

While it might not be critical to include such information for the purposes of this Opinion *per se*, we cannot overlook inconsistencies and inappropriate analyses that would have been avoided if the methodology was clear and well-defined to both the reader and the Committee.

On the one hand (page 12, lines 36-38), the WOE for second-hand exposure assessment is judged to be '*weak-to-moderate*' based on data, the consistency of which is judged to be '*low*'. On the other hand, (page 15, lines 40-43), it is stated that the overall WOE for risk for other long-term adverse health effects, such as pulmonary disease and CNS- and reprotoxic effects, cannot be established 'due to lack of consistent data'.

In both cases, the consistency of data is judged to be low but in one case, WOE is judged weak-to-moderate and in the other case, it 'cannot be established due to lack of consistent data'.

It is important to note that these discrepancies were also found between statements in the abstract and more detailed explanations in the text as well. Page 2, line 9 states "*the overall weight of evidence for risks of local irritative damage to the respiratory tract is: i) moderate for heavy users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine*,…" while page 47, line 14 states that *"If assessed, acute mouth / throat irritation, and cough are reported by a sub-group of users (Polosa et al., 2011; Palamidas et al., 2017) and that these effects are not attributed to the nicotine content (Palamidas et al., 2017).*

Similarly, there is a discrepancy between the conclusion in the abstract that "*the overall weight of evidence for risks of long-term systemic effects on the cardiovascular system is strong,*" (page 2, line 13) and the statement within the text of health effects section, where it actually says the European Heart Network concluded that …"*the long-term effects on the cardiovascular system are still unknown due to the lack of relevant data*" (page 47, lines 28-36).

The definition of '*moderate*' evidence, provided by NASEM, suggests that a general conclusion can be made, but limitations cannot be ruled out with reasonable confidence.[9] Therefore it is questionable as to why the Opinion acknowledges a lack of consistent data, but rates the WOE as weak to moderate.

Furthermore, in assessing the WOE and incidence of health concerns, the Committee acknowledges that: "*The overall weight of evidence for risk of poisoning and injuries due to burns and explosion, is strong,*" implying that there is consistency of data for reported incidents, but the discussion goes on to state that "*However, the incidence is low. Therefore, the risk is expected to be low.*" The Opinion then dedicates a significant discussion to a risk that is acknowledged to be rare and modifiable (pages 50-51, 52-53).

[8] For guidance in weighting of evidence, see EFSA Scientific Committee, Hardy A, Benford D, Halldorsson T, et al., 2017. Scientific Opinion on the guidance on the use of the weight of evidence approach in scientific assessments. EFSA Journal 2017;15(8):4971, 69 pp. https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/j.efsa.2017.4971

[9] NASEM, 2018. Pp 50.

These discrepancies in the Opinion are confusing and bias the overall assessment of the public health impacts (taking into account both risks and benefits) of e-cigarettes.

The importance of this Opinion in shaping tobacco and nicotine regulation for the EU – and its global influence – requires that the Committee takes measures to ensure objective and accurate analysis of the three main points of consideration outlined in the Summary. The following sections will highlight our critique of where and how the Committee failed to meet this obligation.

Scientific Critique

6.5.1 Consumer Behaviour related to exposure assessment

Page 26, lines 27-47*: Use in young populations, children and adolescents*

Underage people should not use or have access to e-cigarettes or any products that contain nicotine. Juul Labs is committed to preventing underage access to e-cigarettes.

The data referenced was collected between 2013 and 2017, during which time (and since), the e-cigarette industry has evolved significantly, as has the evolution of relevant regulation. For instance, until May 2016, the specific rules of the Tobacco Products Directive (TPD) 2 were not fully enforced within the European Union and the previous TPD did not contain specific rules on e-cigarettes. In light of this, devices currently available to consumers, their design features and specific characteristics, should be properly analysed and categorised and should only include data post relevant regulation (post May 2016).

The Opinion notes at line 37 that "*the proportion of youth who reported ever using e-cigarettes varies substantially across surveys*." That finding alone requires the highest prudence when inferences, conclusions and/or policy recommendations based on such large data spread are drawn.

6.5.4 Human evidence for health impacts of electronic cigarettes

A complete understanding of possible health effects of e-cigarettes requires proper assessment of both absolute risk and the risk relative to a relevant comparator, i.e. combustible cigarettes, which e-cigarettes are designed to replace.

Due to the exclusion of consideration for relative risk, many studies evaluating health metrics in smokers who have switched to e-cigarettes were notably missing. The Committee did not discuss several studies and systematic reviews indicating the individual health benefits gained among those who transition away from combustible cigarettes[10] or population level benefits gained if e-cigarettes completely replace combustible cigarettes.[11]

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[10] Polosa R, Morjaria JB, Caponnetto P, et al. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. Respir Res. 2016;17(1):166.
Polosa R, Morjaria JB, Prosperini U, et al. Health effects in COPD smokers who switch to electronic cigarettes: a retrospective-prospective 3-year follow-up. Int J Chron Obstruct Pulmon Dis. 2018;13:2533-2542.
Polosa R, Morjaria JB, Prosperini U, et al. COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. Ther Adv Chronic Dis. 2020;11:2040622320961617.

[11] Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515-523.

Furthermore, the Opinion's reliance on review articles rather than primary sources is problematic, as evidenced by failures to report key aspects of the primary cited literature, inclusion of effects attributed to combustible cigarettes rather than e-cigarettes and improper citation chains that result in statements of conclusion that were not made in the original text.

Acute Effects

Page 47, line 13 which states that a sub-population of users experience acute mouth/throat irritation, and cough and cite Polosa 2011 and Palamida 2017.[12] In the original paper Polosa is careful to point out, however, that these acute effects are short-lived, decreasing substantially from week 4 onwards. In addition, the main results of the most updated version of the Cochrane review on e-cigarettes for cessation corroborates Polosa by reporting that although throat/mouth irritation were among the most commonly reported acute effects, they "*tended to dissipate over time with continued use*."[13]

Cardiovascular Diseases

Page 48, lines 6-7 suggest that e-cigarettes have detrimental effects on heart rate and blood pressure. While these acute changes in BP and HR have been shown to be attributed solely to nicotine,[14] two of the references provided by the review cited in this section, when examined in full, report that e-cigarettes increase heart rate to a much lesser extent than combustible cigarettes.[15] Vlachopoulos demonstrates that e-cigarette users had to use the product for 6x longer to approach the increases in HR and BP observed after smoking one conventional cigarette. Other studies which have reported similar increases in HR after acute usage, noted that these increases were smaller in comparison to those induced by use of combustible cigarettes.[16]

Levy DT, Borland R, Lindblom EN, et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. Tob Control. 2018;27(1):18-25.

[12] Palamidas A, Tsikrika S, Katsaounou PA, et al. Acute effects of short-term use of ecigarettes on Airways Physiology and Respiratory Symptoms in Smokers with and without Airway Obstructive Diseases and in Healthy non-smokers. Tob Prev Cessat. 2017;3:5.

Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. BMC Public Health. 2011;11:786.

[13] Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2020;10:CD010216.

[14] Antoniewicz L, Brynedal A, Hedman L, Lundback M, Bosson JA. Acute Effects of Electronic Cigarette Inhalation on the Vasculature and the Conducting Airways. Cardiovasc Toxicol. 2019;19(5):441-450.

Chaumont M, de Becker B, Zaher W, et al. Differential Effects of E-Cigarette on Microvascular Endothelial Function, Arterial Stiffness and Oxidative Stress: A Randomized Crossover Trial. Sci Rep. 2018;8(1):10378.

[15] Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of Electronic Cigarettes on the Cardiovascular System. J Am Heart Assoc. 2017;6(9).

Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. J Am Coll Cardiol. 2016;67(23):2802-2803.

Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. Regul Toxicol Pharmacol. 2015;71:24–34.

[16] Franzen KF, Willig J, Cayo Talavera S, et al. E-cigarettes and cigarettes worsen peripheral and central hemodynamics as well as arterial stiffness: A randomized, double-blinded pilot study. Vasc Med. 2018;23(5):419-425.

Page 48, lines 5-9 are written in such a way that a reader could infer that Moheimani et al provides direct evidence of atomized nicotine inducing arrhythmia. Moheimani and colleagues report that habitual e-cigarette use is associated with a shift toward sympathetic predominance.[17] The report of Moheimani et al includes 62.5% (10/16) former smokers however, likely confounding the results. Although inclusion criteria required that participants must have quit >1 year prior to the study, the effects of combustible cigarettes are long lasting. A prospective study with data from 1954 to 2014 indicated that 10-15 years of smoking cessation is needed for former smoker's risk of CVD to decrease to that of non-smokers.[18] It is therefore not possible to delineate whether the results of Moheimani are confounded by the effect of former smoking on the cardiovascular system.

Page 48, lines 41-45 state that "*According to the literature, the level of evidence regarding the underlined mechanisms is considered from moderate to strong. It could be assumed that similar mechanisms exist regarding electronic cigarettes use (Benowitz et al., 2016).*"[19] SCHEER attributes levels of strength (moderate to strong) to the evidence for the underlined mechanisms Benowitz provides for the CV effects in Table 8. This attribution is not supported by the referenced literature. Benowitz makes no claim to the strength of the data provided and, at times, clarifies that the evidence is unclear. For example, with regard to nicotine's effect on endothelial function Benowitz states, "*it is unclear how important nicotine is compared to the powerful effects of oxidants and pro-inflammatory agents*."

With regard to lipid abnormalities, Benowitz makes no reference to triglycerides in his paper and states that although it is reasonable to infer a link between nicotine and a more atherogenic lipid profile, "*multiple cessation studies using nicotine medications (NRT and nicotine nasal spray) report reduced dyslipidemia with sig-nificant improvement in HDL/LDL ratios*." Overall, the effects outlined in Table 8 are either considered as possibilities (the effects could be possible or are biologically plausible) or have only been demonstrated in animals in the reference papers. While haemodynamic effects of nicotine are well-characterized, the only other effect Benowitz et al, suggest is actually evident is insulin resistance. Indeed, Benowitz et al. conclude that population-level benefits could be gained if e-cigarettes replace combustible cigarettes: "*If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be substantially reduced and there would likely be a substantial net benefit for cardiovascular health*."[20]

Lung Diseases

Szoltysek-Boldys I, Sobczak A, Zielinska-Danch W, Barton A, Koszowski B, Kosmider L. Influence of inhaled nicotine source on arterial stiffness. Przegl Lek. 2014;71(11):572-575.

Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. J Am Coll Cardiol. 2016;67(23):2802-2803.

[17] Moheimani RS, Bhetraratana M, Peters KM, et al. Sympathomimetic Effects of Acute E-Cigarette Use: Role of Nicotine and Non-Nicotine Constituents. J Am Heart Assoc. 2017;6(9).

[18] Duncan MS, Freiberg MS, Greevy RA, Jr., Kundu S, Vasan RS, Tindle HA. Association of Smoking Cessation With Subsequent Risk of Cardiovascular Disease. JAMA. 2019;322(7):642-650.

[19] Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26(6):515-523.

[20] ibid

The Committee's evaluation of the lung impacts from ENDS use (page 49, lines 2-20) focuses on reviews of in vitro studies that did not use a combustible cigarette control and/or used ENDS aerosol exposure that is unlikely to be relevant to human use. A response published in 2018 regarding the use of in vitro studies of e-cigarette aerosol to conclude effects in humans stated "*The present study does not replicate normal conditions of use and lacks standardized protocols for E-cigarette aerosol exposure and dosimetry. To this regard, animal studies and in vitro systems often include chronic, high-dose exposures and do not approximate the type of exposure from human vaping, thus leading to extreme overestimation of toxicological effects.*"[21]

Furthermore, as previously stated, this section omitted review of several studies examining lung function in smokers who have switched from combustible products to e-cigarettes. A study from 2016 evaluating health metrics of smokers diagnosed with COPD demonstrates that smokers who switched to e-cigarettes showed significant increases in exercise capacity and decreases in COPD exacerbations and reversal of lung capacity decline over a two-year period. Follow up studies published in 2018 and 2020 showed continuing trends in this population at years 3 and 5.[22] Importantly, this study concludes that "*The present study suggests that EC use may ameliorate objective and subjective COPD outcomes, and that the benefits gained appear to persist long term. [E-Cigarette] use for abstinence and smoking reduction may ameliorate some of the harm resulting from tobacco smoking in COPD patients*."

Second-hand exposure

Page 51, lines 27-55: Many of the citations in this section providing evidence of the risks associated with second-hand exposure reference combustible cigarettes, not e-cigarettes.[23] Given the lack of data on second-hand exposure from e-cigarettes, it is inappropriate to draw conclusions from second-hand exposure of combustible cigarettes and apply them to e-cigarettes. In fact, one study not discussed in this Opinion demonstrated that measured particulate matter ($PM_{2.5}$) in households with e-cigarette use was similar to non-smoking households and was 58 times lower than household environments following smoking.[24]

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[21] Li Volti G, Polosa R, Caruso M. Assessment of E-cigarette impact on smokers: The importance of experimental conditions relevant to human consumption. Proc Natl Acad Sci U S A. 2018;115(14): E3073-E3074.

[22] Polosa R, 2016
Polosa R, 2018
Polosa R, 2020

[23] Dunbar A, Gotsis W, Frishman W. Second-hand tobacco smoke and cardiovascular disease risk: an epidemiological review. Cardiol Rev. 2013;21(2):94-100.
He J, Vupputuri S, Allen K, Prerost MR, Hughes J, Whelton PK. Passive smoking and the risk of coronary heart disease--a meta-analysis of epidemiologic studies. N Engl J Med. 1999;340(12):920-926.
Law MR, Morris JK, Wald NJ. Environmental tobacco smoke exposure and ischaemic heart disease: an evaluation of the evidence. BMJ. 1997;315(7114):973-980.
Lv X, Sun J, Bi Y, et al. Risk of all-cause mortality and cardiovascular disease associated with second-hand smoke exposure: a systematic review and meta-analysis. Int J Cardiol. 2015;199:106-115.

[24] Fernandez E, Ballbe M, Sureda X, Fu M, Salto E, Martinez-Sanchez JM. Particulate Matter from Electronic Cigarettes and Conventional Cigarettes: a Systematic Review and Observational Study. Curr Environ Health Rep. 2015;2(4):423-429.

This section (page 51, line 41-42) also states that there is only one paper evaluating passive exposure, demonstrating increased levels of ambient air nicotine and biomarkers of nicotine.[25] This study, conducted in 2011, demonstrated increased ambient air nicotine concentrations, but the Opinion does not mention one of the main findings, that airborne markers were 5.7 times higher in homes with combustible cigarette smokers than those with e-cigarette users.

The SCHEER Opinion twice cites a paper by Shearston et al.[26] as evidence that e-cigarette use results in second-hand exposure of nicotine (page 51, lines 35-39). However, this paper is a protocol for a study which has not yet reported any findings.

Page 52, lines 5-10 In discussing the implications of third-hand smoke from e-cigarettes, the Opinion cites a review from Diez-Izquierdo, 2018[27] which the Committee acknowledges concludes: "*that only speculations can be made on the long-term effects of these exposures*." In fact, this review only cited one in-home (natural setting) study that showed no significant differences in nicotine levels on surfaces in the homes of e-cigarette users compared to non-smokers/non-e-cigarette users.[28]

Other health effects

The Opinion dedicated extensive discussion regarding nicotine poisoning and fires and burns resulting from e-cigarette explosions (Pages 50-51 and pages 52-54). While we appreciate the need to address any adverse health event, the extremely rare occurrences of each of these adverse health effects was only briefly mentioned as were the regulatory policies that can substantially decrease incidence of such events, including the adoption of battery safety standards for devices and child-tamper resistant standards for containers and pods.[29]

Finally, the reliance of review articles and the resulting citation chains appear to have resulted in misinterpretation of absolute risks.

Page 48, line 9 suggests that e-cigarettes will result in long-term adverse impacts on vasculature citing a review article by Zhang, 2018.[30] But there is no evidence of that in the cited review. The review reports

[25] Ballbe M, Martinez-Sanchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. Environ Res. 2014;135:76-80.

[26] Shearston J, Lee L, Eazor J, et al. Effects of exposure to direct and second-hand hookah and e-cigarette aerosols on ambient air quality and cardiopulmonary health in adults and children: protocol for a panel study. BMJ Open. 2019;9(6):e029490.

[27] Diez-Izquierdo A, Cassanello-Penarroya P, Lidon-Moyano C, Matilla-Santander N, Balaguer A, Martinez-Sanchez JM. Update on thirdhand smoke: A comprehensive systematic review. Environ Res. 2018;167:341-371.

[28] Bush D, Goniewicz ML. A pilot study on nicotine residues in houses of electronic cigarette users, tobacco smokers, and non-users of nicotine-containing products. Int J Drug Policy. 2015;26(6):609-611.

[29] Article 20 of the Tobacco Products Directive (2014/40/EU), "E-cigarettes should be child-resistant and tamper evident and have a mechanism that allows refilling without spillage to protect consumers."

[30] Zhang G, Wang Z, Zhang K, et al. Safety Assessment of Electronic Cigarettes and Their Relationship with Cardiovascular Disease. Int J Environ Res Public Health. 2018;15(1).

the thoughts of *Professor Choupo Perk*, which in turn are cited to be a work by Ying Zhang, which in turn is citing the results of another paper which was not accessible at this time.[31]

Page 47, line 44 indicates that the US FDA has "*highlighted the adverse health impacts of electronic cigarette use*" and cites Chen 2013. However, the citation provided is a one-page summary that does not contain any data or references on the health effects of e-cigarettes.[32]

The citation chains highlighted above are improper and found throughout (see also, section 6.6 page 66, lines 28-30**)**, the Opinion should provide a reference with direct evidence of the claim being made rather than utilising a difficult chain of citations that do not provide the evidence for what the Opinion is proposing.

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

Flavours

Flavours are extensively discussed on pages 64-66. The summary concludes that flavours are a primary reason to initiate vaping. This does not comport with other data demonstrating that the primary reason to use e-cigarettes is as an alternative to cigarettes.[33] It is also contradictory to the statement on Page 64, lines 2-4, that in the EU, according to Eurobarometer 458, the most frequently mentioned reason for taking up e-cigarettes is to stop or reduce tobacco use.[34]

The evidence suggests that not only is quitting smoking the primary reason to initiate vaping, but that flavours help adult smokers switch and stay away from cigarettes.

While smokers generally start using tobacco flavours, over time, flavour preferences change to non-tobacco flavours, particularly dessert or sweet flavours. Gendall, 2020, showed that adult smokers who partly or completely switched to e-cigarettes, the most preferred flavour e-liquid was fruit.[35]

A randomised controlled trial showed that e-cigarettes are twice as effective as NRTs at helping smokers quit and that when allowed to choose, smokers initially given tobacco flavoured e-liquids chose other flavours. By the end of the study, tobacco and menthol represented ~41% and other flavours represented ~59% of product use.[36]

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[31] Zhang Y. Evidence for Research on the Harm of E-cigarettes. Guangxi Quality Supervision Guide. Periodical. 2017;3:9.

[32] Chen IL. FDA summary of adverse events on electronic cigarettes. Nicotine Tob Res. 2013;15(2):615-616.

[33] Nicksic NE, Snell LM, Barnes AJ. Reasons to use e-cigarettes among adults and youth in the Population Assessment of Tobacco and Health (PATH) study. Addict Behav. 2019;93:93-99.
Patel D, Davis KC, Cox S, et al. Reasons for current E-cigarette use among U.S. adults. Prev Med. 2016;93:14-20.

[34] Special Eurobarometer 458 "Attitudes of Europeans towards tobacco and electronic cigarettes" European Union, 2017 Survey conducted by TNS political&social at the request of the European Commission, Directorate-General for Health and Food safety (DG SANTE)

[35] Gendall P, Hoek J. Role of flavours in vaping uptake and cessation among New Zealand smokers and non-smokers: a cross-sectional study. Tob Control. 2020.

[36] Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med. 2019;380(7):629-637.

We question why the majority of the cited literature relates to only US products, which are neither TPD-compliant nor available in the EU. Quotes are lifted directly from review articles that include very little original synthesis[37] or are irrelevant to e-cigarette use[38] and much of the relevant literature has been omitted.[39]

Page 66, lines 7-9 state that "*Whereas flavours are added to increase product liking, addictive substances such as nicotine play a role in motivation and influence the reward system through mechanisms of learning and wanting (in Krusemann, et al., 2018)*." This is an incorrect interpretation of 'liking' and 'wanting' theories of addiction. Liking versus Wanting is a theory that distinct neuronal mechanisms are involved in each subjective effect and that liking may promote excessive wanting through increased sensitization of the dopaminergic systems that drive addiction.[40] Liking versus Wanting is not about subjective characteristics of substances that make them user-friendly or appealing (in this case flavours).

Nicotine

Page 66, line 12 states that '*the high concentrations of nicotine in electronic cigarettes are of major concern'*. Most research demonstrates that at nicotine concentrations permissible in the EU, nicotine concentrations in the blood are well below that from combustible cigarette use. In fact, O'Connell et al., cited on page 66, line 35, reports that e-cigarettes with nicotine levels twice that permissible in the EU (myblu 40mg) delivered approximately 33% less nicotine to the user than a combustible cigarette. A TPD-compliant version (myblu 16%) delivered less than half that of a combustible cigarette.[41] Smoking is a major concern, and while nicotine is an addictive component, the majority of the harm of smoking is caused by other constituents. E-cigarettes provide nicotine without these harmful constituents, thereby

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[37] Walley SC, Wilson KM, Winickoff JP, Groner J. A Public Health Crisis: Electronic Cigarettes, Vape, and JUUL. Pediatrics. 2019;143(6).

[38] Hoffman AC, Salgado RV, Dresler C, Faller RW, Bartlett C. Flavour preferences in youth versus adults: a review. Tob Control. 2016;25(Suppl 2):ii32-ii39.

[39] Chen JC. Flavored E-cigarette Use and Cigarette Smoking Reduction and Cessation-A Large National Study among Young Adult Smokers. Subst Use Misuse. 2018;53(12):2017-2031.
Glasser A, Vojjala M, Cantrell J, et al. Patterns of e-cigarette use and subsequent cigarette smoking cessation over two years (2013/2014 to 2015/2016) in the Population Assessment of Tobacco and Health (PATH) Study. Nicotine Tob Res. 2020.
Gravely S, Cummings KM, Hammond D, et al. The Association of E-cigarette Flavors With Satisfaction, Enjoyment, and Trying to Quit or Stay Abstinent From Smoking Among Regular Adult Vapers From Canada and the United States: Findings From the 2018 ITC Four Country Smoking and Vaping Survey. Nicotine Tob Res. 2020;22(10):1831-1841.
Jones DM, Ashley DL, Weaver SR, Eriksen MP. Flavored ENDS Use among Adults Who Have Used Cigarettes and ENDS, 2016-2017. Tob Regul Sci. 2019;5(6):518-531.

[40] Berridge KC, Robinson TE. Liking, wanting, and the incentive-sensitization theory of addiction. Am Psychol. 2016;71(8):670-679.

[41] O'Connell G, Pritchard JD, Prue C, et al. A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profiles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers. Intern Emerg Med. 2019;14(6):853-861.

preventing most of the harm. But to successfully compete with cigarettes, e-cigarettes must deliver sufficient nicotine.

Page 66, lines 28-30 cite a review that suggests that adolescents who vape are exposed to more nicotine than those who smoke.[42] This review combined results from two different studies, by different investigators, and using different study protocols.[43] In one study, the values used are not published, cannot be verified and are not accessible in the supplementary files.[44]

Renormalization and Gateway

Two key studies omitted from this section of the Preliminary Opinion report that there is "*little evidence that renormalisation of youth smoking was occurring during a period of rapid growth and limited regulation of e-cigarettes from 2011 to 2015*" in the UK and that smoking prevalence among UK youth decreased even further from 2018-19, even as vaping increased.[45]

The assertion on page 70, line 12**,** that there is strong evidence that '*e-cigarettes are a gateway to smoking/for young people*' is not borne out by the evidence. Despite a reliance on US literature, there is no reference to decreases in smoking in the US, as vaping increases, including with adolescents. NASEM 2018 reported that although e-cigarette use increases the likelihood of ever trying a cigarette, this did not cause an increase in smoking but a rapid decline in adolescent smoking has been observed.[46] In fact, more recent prevalence data from the ITC (Hammond 2020), that are not cited or included in this section, show that smoking prevalence among UK youth and young adults decreased even further from 2018 to 2019, even as vaping prevalence slightly increased.[47]

6.7 Cessation of traditional smoking

The best option for smokers would be to quit all tobacco and nicotine and nicotine products. We agree that it is '*essential to implement strategies that help smokers in quitting*' (page 70, lines 27-29)**.** But the vast majority of smokers in the EU are not quitting. The 2020 EUREST-PLUS ITC Europe Surveys[48] show that in all countries studied, the majority of smokers say that they have not tried to quit smoking in the

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[42] Walley, 2019

[43] Benowitz NL, Nardone N, Jain S, et al. Comparison of Urine 4-(Methylnitrosamino)-1-(3)Pyridyl-1-Butanol and Cotinine for Assessment of Active and Passive Smoke Exposure in Urban Adolescents. Cancer Epidemiol Biomarkers Prev. 2018;27(3):254-261.
Goniewicz ML, Boykan R, Messina CR, Eliscu A, Tolentino J. High exposure to nicotine among adolescents who use Juul and other vape pod systems ('pods'). Tob Control. 2019;28(6):676-677.

[44] Benowitz, 2018

[45] Hallingberg B, Maynard OM, Bauld L, et al. Have e-cigarettes renormalised or displaced youth smoking? Results of a segmented regression analysis of repeated cross-sectional survey data in England, Scotland and Wales. Tob Control. 2020;29(2):207-216.

[46] NASEM, 2018.

[47] Hammond D, Rynard VL, Reid JL. Changes in Prevalence of Vaping Among Youths in the United States, Canada, and England from 2017 to 2019. JAMA Pediatr. 2020.

[48] Papadakis S, Katsaounou P, Kyriakos CN, et al. Quitting behaviours and cessation methods used in eight European Countries in 2018: findings from the EUREST-PLUS ITC Europe Surveys. Eur J Public Health. 2020;30(Supplement_3): iii26-iii33.

previous 12 months, have never tried to quit smoking and do not intend to in the next 6 months. An exception is England, which has one of highest reported quitting rates in the EU and where e-cigarettes are the most popular self-reported quitting aid.

The results of the 2020 UCL Smoking Toolkit Study shows that the proportion of people who have successfully quit smoking this year in England is at its highest in more than a decade. Quitting success rates have increased by almost two-thirds, and smoking prevalence in England is at an all-time low.[49]

Papadakis et al. 2020 conclude that approaches to quitting smoking need to be re-examined in the EU including increasing the use of quit support.[50] They note that in the UK where e-cigarette use is supported by the government and public health bodies, more than half of quit attempts are made with the help of e-cigarettes, demonstrating the relationship between e-cigarette use, successful quitting and a receptive regulatory environment.

Given that smokers in the EU are not quitting, any plateau/declines are likely a consequence of young people not starting rather than smokers quitting. This means that there is an aging population of hard-to-reach smokers who are now at increasing risk of severe and potentially fatal illness onset in their later years. Millions of smokers across the EU are now, therefore, most at risk of developing an avoidable cancer and therefore would benefit greatly from the Commission's Beating Cancer Plan prevention efforts.

The conclusion of the 2020 US Surgeon General report that e-cigarettes, in general, does not increase smoking cessation (page 71, lines 21-28) is at odds with the results of a US National Institutes of Health-funded study, which concluded that the first statistically significant increase in population smoking cessation in the US in nearly a quarter of a century was associated with a substantial increase in ENDS use among US adults.[51]

We disagree that there is a lack of robust data on the effect of e-cigarettes on smoking cessation (page 71, lines 33-34). In the hierarchy of evidence, randomised controlled trials (RCTs) represent the gold standard of scientific research. Several RCTs show that e-cigarettes clearly displace smoking,[52] a finding that is supported by Population Studies, Observational studies, and Scientific Reviews.[53] The most

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[49] Smoking in England – top line findings. Ref. STS140121 http://www.smokinginengland.info/latest-statistics/

[50] Papadakis S, et al., (2020).

[51] Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ. 2017;358:j3262.

[52] Hajek P, Phillips-Waller A, Przulj D, et al. A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy. N Engl J Med. 2019;380(7):629-637.
Hatsukami DK, Meier E, Lindgren BR, et al. A Randomized Clinical Trial Examining the Effects of Instructions for Electronic Cigarette Use on Smoking-Related Behaviors and Biomarkers of Exposure. Nicotine Tob Res. 2020;22(9):1524-1532.
Walker N, Parag V, Verbiest M, Laking G, Laugesen M, Bullen C. Nicotine patches used in combination with e-cigarettes (with and without nicotine) for smoking cessation: a pragmatic, randomised trial. Lancet Respir Med. 2020;8(1):54-64.

[53] Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ. 2017;358:j3262.

recent review by the Cochrane Collaboration, a stalwart of evidence-based medicine, confirmed their earlier finding that e-cigarettes help people quit smoking.[54]

6.5.2 Exposure assessment

Overall, a robust analysis of appropriate exposure assessment studies is lacking, and this analysis of risk exposure studies ignored swathes of published literature.

With regard to aerosol characteristics, this section reaches a conclusion that is based on only a small selection of the available scientific literature. The section omitted numerous other measurements of the particle size distribution from e-cigarettes that have been published[55] including one that has attempted to address e-cigarette aerosol dilution in the measurement of the particle size distribution. [56] Furthermore, the discussion of aerosol characteristics including particle number concentration and particle size distribution lacks understanding of the semi-volatile nature of e-cigarette aerosol that exists in the scientific literature - specifically, how instrument limitations in measurement of concentrated temporally dynamic aerosols affect the resulting measurements of particle size distribution and geometric standard deviation. This has been discussed in detail by Ingebrethsen et al. (2012) noting that complications in measurement of particle size distribution of tobacco burning are exacerbated for e-cigarettes due to comparably large number concentrations and higher volatility of the particulate matter.[57]

We note that conclusions regarding second-hand exposure (beginning on page 38, line 14) were reached using only three cited studies. Detailed analysis from one study is specific to three device/formulation

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Jackson SE, Beard E, Kujawski B, et al. Comparison of Trends in Self-reported Cigarette Consumption and Sales in England, 2011 to 2018. JAMA Netw Open. 2019;2(8):e1910161.
McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England. London: Public Health England.

[54] Hartmann-Boyce J, McRobbie H, Lindson N, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2020;10:CD010216.

[55] Bertholon JF, Becquemin MH, Roy M, et al. [Comparison of the aerosol produced by electronic cigarettes with conventional cigarettes and the shisha]. Rev Mal Respir. 2013;30(9):752-757.
Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. Environ Pollut. 2014;184:523-529.
Marini S, Buonanno G, Stabile L, Ficco G. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. Toxicol Appl Pharmacol. 2014;278(1):9-15.
McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol. 2012;24(12):850-857.
Mikheev VB, Brinkman MC, Granville CA, Gordon SM, Clark PI. Real-Time Measurement of Electronic Cigarette Aerosol Size Distribution and Metals Content Analysis. Nicotine Tob Res. 2016;18(9):1895-1902.
Montigaud Y, Aerosol regional deposition of electronic cigarette emissions using an original *ex vivo* respiratory model. Journal of Aerosol Science Volume 151, January 2021.
Zhang Y, Sumner W, Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. Nicotine Tob Res. 2013;15(2):501-508.

[56] Oldham MJ, Zhang J, Rusyniak MJ, Kane DB, Gardner WP. Particle size distribution of selected electronic nicotine delivery system products. Food Chem Toxicol. 2018;113:236-240.

[57] Ingebrethsen BJ, Cole SK, Alderman SL. Electronic cigarette aerosol particle size distribution measurements. Inhal Toxicol. 2012;24(14):976-984.

combinations.[58] Notably, the tested combinations did not include pod-based products (See Table 1 of Visser et al., 2019) which are extensively discussed throughout the SCHEER Opinion. Studies that were omitted from consideration include those that measured air concentrations of selected constituents where e-cigarettes are or have been used[59] including those that analyse biomarkers of exposure.[60] There are also numerous studies that examine constituents in exhaled breath that were omitted from consideration in the Opinion.[61]

If the substantial number of studies on second-hand exposure were to be included in this analysis, the authors might reach a different conclusion regarding the WOE. The objective evaluation of all of these studies also is consistent with the following conclusion in the Exposure Assessment section of the SCHEER Opinion (page 39, lines 13-14): "*The reported concentrations are orders of magnitude lower for all these substances than those reported for exposure of electronic cigarette users*." We believe that there is high consistency in the data from chamber studies where individuals are vaping and exhaled breath studies since the vast majority reach the same conclusions (see above conclusion). Based upon the additional studies we have provided, we strongly disagree that there is a scarcity of data (page 39, line 18) and believe that the similar conclusions from these studies that use different exposure scenarios, device designs, topography, and liquid compositions provide a robust data set that provides a

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[58] Visser WF, Klerx WN, Cremers H, Ramlal R, Schwillens PL, Talhout R. The Health Risks of Electronic Cigarette Use to Bystanders. Int J Environ Res Public Health. 2019;16(9).

[59] Institute for Occupational Safety and Health, Health Hazard Evaluation Report 2015-0107-3279.
Ballbe M, Martinez-Sanchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. Environ Res. 2014;135:76-80.
Khachatoorian C, Jacob P, 3rd, Sen A, Zhu Y, Benowitz NL, Talbot P. Identification and quantification of electronic cigarette exhaled aerosol residue chemicals in field sites. Environ Res. 2019;170:351-358.
Nguyen C., Li L., Sen C.A., Ronquillo E., Zhu Y. Fine and ultrafine particles concentrations in vape shops. Atmos. Environ. 2019;211:159–169.
Zwack LM, Stefaniak AB, LeBouf RF, 2017. Evaluation of chemical exposures at a vape shop, Health, Hazard Evaluation Report, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National

[60] Chorti M et al., Effects of active and passive electronic and tobacco cigarette smoking on lung function, Toxicology Letters (2011)
Flouris AD, Poulianiti KP, Chorti MS, et al. Acute effects of electronic and tobacco cigarette smoking on complete blood count. Food Chem Toxicol. 2012;50(10):3600-3603.
Johnson JM, Naeher LP, Yu X, et al. A biomonitoring assessment of secondhand exposures to electronic cigarette emissions. Int J Hyg Environ Health. 2019;222(5):816-823.
Kostikas K, Minas M, Nikolaou E, et al. Secondhand smoke exposure induces acutely airway acidification and oxidative stress. Respir Med. 2013;107(2):172-179.

[61] Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. Int J Environ Res Public Health. 2014;11(11):11177-11191.
Marco E, Grimalt JO. A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers. J Chromatogr A. 2015;1410:51-59.
Papaefstathiou E, Stylianou M, Andreou C, Agapiou A. Breath analysis of smokers, non-smokers, and e-cigarette users. J Chromatogr B Analyt Technol Biomed Life Sci. 2020;1160:122349.
Samburova V, Bhattarai C, Strickland M, et al. Aldehydes in Exhaled Breath during E-Cigarette Vaping: Pilot Study Results. Toxics. 2018;6(3).
St Helen G, Havel C, Dempsey DA, Jacob P, 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 2016;111(3):535-544.

high degree of confidence in the conclusions. We believe that objective evaluation of all of these studies, especially those that contain contemporaneous comparison to combustible cigarettes provides a consistent conclusion that except for propylene glycol and glycerine, the potential constituent exposure to exhaled constituents and particulate matter are orders of magnitude less than from combustible cigarettes.

6.5.3 Hazard identification of most relevant compounds

Page 39, lines 34-45: This section, which cites papers by Khlystov and Samburova, 2016 and Vreeke et al. 2018, states that e-cigarette aerosols contain pyrolysis products including aldehydes that can be toxic and affect different organs.[62] Khlystov and Samburova is not consistent, however, with other similar studies (aldehydes of mg/puff versus mg or ng/puff) and is not appropriate for hazard identification in this case. This inconsistency and the fact that no other study had detected such an effect has been noted in a response to the original study.[63]

While recent publications have also recorded the presence of aldehydes in some e-cigarette aerosols, they record aldehydes at levels that are at maximum 100-fold less[64] than those reported by Khlystov and Samburova, 2016. As the Opinion notes in the Exposure Assessment (6.5.2, page 38, lines 1-2), "*The higher carbonyl levels in several studies most probably are generated under dry puff conditions and can be considered unusable for the risk assessment.*" As such, this same principle should be applied to section 6.5.3.

Page 40, line 33 - Page 41, line 16 considers relevant oxidation products, such as formaldehyde, acetaldehyde and acrolein.

This section is confusing especially in context with the data presented in Table 5 of section 6.5.2. It appears that the intent of presenting the information in this manner is to compare the values for exposure limits presented on page 40, lines 33-41 to the values found in Table 5. The exposure limits presented in this section are for room air, not per puff exposure limits and this is not adequately

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[62] Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. Environ Sci Technol. 2016;50(23):13080-13085.
Vreeke S, Peyton DH, Strongin RM. Triacetin Enhances Levels of Acrolein, Formaldehyde Hemiacetals, and Acetaldehyde in Electronic Cigarette Aerosols. ACS Omega. 2018;3(7):7165-7170.

[63] Farsalinos K, Gillman G, Kistler K, Yannovits N. Comment on "Flavoring Compounds Dominate Toxic Aldehyde Production during E Cigarette Vaping". Environ Sci Technol. 2017;51(4):2491-2492.

[64] Conklin DJ, Ogunwale MA, Chen Y, et al. Electronic cigarette-generated aldehydes: The contribution of e-liquid components to their formation and the use of urinary aldehyde metabolites as biomarkers of exposure. Aerosol Sci Technol. 2018;52(11):1219-1232.
Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 2018;113(11):2099-2106.
Farsalinos KE, Kistler KA, Pennington A, Spyrou A, Kouretas D, Gillman G. Aldehyde levels in e-cigarette aerosol: Findings from a replication study and from use of a new-generation device. Food Chem Toxicol. 2018;111:64-70.
Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res. 2014;16(10):1319-1326.
Sleiman M, Logue JM, Montesinos VN, et al. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. Environ Sci Technol. 2016;50(17):9644-9651.

explained in this section. While this section includes permissible exposure limits (in units of mg/M3) it does not reference any way to correctly compare these values to the data presented in Table 3 or 5 which are calculated differently. The work by Flora 2016 provides guidance on how to compare permissible exposure limits to e-vapour product yields.[65]

We recommend that a pre-section be added to 6.5.3 that addresses how one might convert exposure limits into a daily exposure amount to facilitate a comparison with Table 3. Without this information, the exposure limits have no context or meaning.

Risk assessment 6.5.5

Page 56, line 33: "*As a pragmatic alternative, the Margin of Exposure (MoE) approach may be applied*."

The MoE section in the Opinion does not allow the reader to determine if the MoEs are accurate. The MoE is calculated as the No Observed Adverse Effect Level (NOAEL) divided by the Estimated Human Exposure (EHE). The NOAEL does not take uncertainty into consideration, necessitating the need for MoE to be compared with Uncertainty Factors (UFs). Where and which UFs were applied for each MoE were not provided making interpretation and appropriate application difficult.[66]

Page 56, lines 40-43: "*In general, only interspecies and inter-individual differences in susceptibility need to be taken into account in the evaluation of the MoE if no adverse effects are observed at the PoD. Typically, an MOE of minimally a factor of 100 is then considered to be required for non-carcinogenic effects.*"

Without knowing the UFs for a particular MoE, the MoE cannot be interpreted and risk cannot be assessed. Please note that the MoE approach would not be appropriate if Health Based Guidance Values (HBGVs), such as RfCs, were used instead of NOAELs. Hazard Quotients should be used with HBGVs.[67]

Page 56, Lines 3-31: Dose metrics in the risk assessment of e-cigarettes.

"*In risk assessment, the hazard information preferably needs to show an exposure regime close to that of the exposure scenario under investigation*.... [to line 31]"

Although toxicity reference values developed for the general and occupational populations are not intended to be used for tobacco product exposure evaluation, they can inform the overall toxicity of tobacco products. As noted by the US FDA in their 2019 memo outlining the Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products,[68] toxicity reference values for the general population are considered to be the most health protective and therefore preferable for estimating any

[65] Flora JW, Wilkinson CT, Wilkinson JW, et al. Method for the Determination of Carbonyl Compounds in E-Cigarette Aerosols. J Chromatogr Sci. 2017;55(2):142-148.

[66] Dankovic DA, Naumann BD, Maier A, Dourson ML, Levy LS. The Scientific Basis of Uncertainty Factors Used in Setting Occupational Exposure Limits. J Occup Environ Hyg. 2015;12 Suppl 1:S55-68.

[67] ibid

[68] U.S. Food & Drug Administration. Memorandum: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products. (2019)

potential hazards and risks. In contrast, the use of Occupational Exposure Limits may only inform the toxicity evaluation for non-cancer effects.

Page 58, Line 54 -57; Page 59, Lines 1-6: "*Several reviews are available that predominantly compare exposure levels of substances in aerosol from e-cigarettes with health-based guidance values …. such risk assessments are not applicable for the purpose of this Opinion, unless they show that the puff concentrations measured are below these standards and therefore clearly point at the absence of any risk with a wide margin*."

The majority of e-cigarette constituents in aerosol, including HPHCs, are at reduced levels or BLOD/BLOQ, indicating substantial lower concentrations in the lungs (peak concentrations) compared to conventional cigarettes. The analytical chemistry data reported by Czekala et al. (2019)[69] show that with the exception of the base e-liquid ingredients, the levels of all measured constituents, including established and proposed HPHCs with known respiratory toxicities are reduced in e-cigarette aerosols compared to smoke from combustible cigarettes.

Czekala reported > 99% reduction in the e-cigarette aerosol of respiratory toxicants including the potent respiratory toxicants acrolein, acrylonitrile and 1,3-butadiene. Among all respiratory toxicants, only the aerosol level of acrolein (peak concentration) exceeds its extremely low reference concentration. The aerosol levels for the remaining constituents with respiratory toxicity were below their respective reference values, suggesting low or no risk for respiratory effects.

Studies from Juul Labs show similar results.[70]

These data indicate that for the majority of the e-cigarette aerosol constituents, peak concentrations of e-cigarette aerosols are below their health-based guidance values.

6.3 European Regulatory Framework

Enabling non-combustible products such as e-cigarettes to compete with cigarettes by delivering nicotine at levels consistent with a cigarette is necessary to facilitate adult smoker switching completely away from cigarettes to potentially less harmful alternatives. This is a critical component of tobacco harm reduction, a concept enshrined in the WHO Framework Convention on Tobacco Control (Art. 1(d)), of which the EU is a signatory.[71]

The Opinion (page 23, lines 11-21) cites TPD recital 38, which states that 20 mg/ml limit on nicotine concentration in e-cigarette liquids "*allows for a delivery of nicotine that is considered to be comparable*

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[69]Lukasz Czekala, Liam Simms, Kathryn Rudd, Georgiana Cava, Matthew Stevenson. Quantitative Risk Assessment (QRA) indicates reduced risk potential for carcinogenic and non-carcinogenic effects of the aerosol of Next Generation Products compared to reference cigarette. CORESTA SSPT Conference, October 6-10, 2019. Hamburg, Germany.

[70] Weil, R et al., Comparative Health Risk Assessment of JUUL System and Combustible Cigarette. *Presented at No Smoke Summit* (2020)

[71] WHO Framework Convention on Tobacco Control. 2003. Article 1(d) states that "'*tobacco control*' *means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke*;" https://www.who.int/tobacco/framework/WHO_FCTC_english.pdf?ua=1

to the permitted dose of nicotine delivery from a standard cigarette." However, the scientific evidence demonstrates that rather than facilitating e-cigarette competition with cigarettes, the 20 mg/ml nicotine cap actually protects cigarettes from competition.

The 20 mg/ml nicotine restriction is based in large part on studies by Prof Farsalinos, who subsequently stated that the Commission "*misinterpreted*" his research and that his data does not support this limit.[72] Subsequent studies support these objections. Hajek et al. (2017) measured nicotine absorption levels in study participants who used e-cigarettes with nicotine concentrations ranging from 16mg/mL to 48mg/mL (nearly 2.5 times the TPD limit), as well as combustible cigarettes.[73] The study showed that in all cases, e-cigarettes delivered less nicotine than the combustible cigarette.

Hajek et al. also found that the device power settings impacted nicotine delivery, suggesting that the current limit may incentivise the use of e-cigarettes that operate at higher temperatures, which deliver more aerosol and thus more nicotine per puff from lower concentration liquids.[74] Increased temperatures and the larger amounts of aerosols produced potentially expose users to increased levels of harmful aerosol constituents.[75] As Hajek et al. noted, even at the highest setting, the highest blood concentration of nicotine was still a third less than that of cigarette, on average, but this comes with greater exposure to harmful and potentially harmful constituents.

This suggests that regulating nicotine delivery on the basis of nicotine concentration alone is not fit for purpose. Other factors including product design and user behaviour also influence nicotine delivery.

Effectively regulating nicotine delivery from e-cigarettes so that they can deliver nicotine in a way that is competitive with cigarettes and ensure a high level of potential health protection for the public means basing restrictions on levels of nicotine absorption, as measured in well-controlled pharmacokinetic studies. Scientific data demonstrate that products with nicotine concentrations at or below 20 mg/ml generally do not deliver nicotine at comparable levels to cigarettes. Products with e-liquid nicotine concentrations below this level could be exempt from this requirement.

Conclusion

To uphold its obligations to protect the health and welfare of its populace, the EU Commission has a duty to consider scientific evidence that may affect the policy positions and outcomes relating to tobacco products and e-cigarettes. We request that the Commission provide a robust analysis of relevant data and look to external reports and counsel to justify their positions – particularly the

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[72] "The European Commission has misinterpreted my scientific research on nicotine in e-cigarettes," by Dr. Konstantinos Farsalinos, January 10, 2014. http://ecigarette-research.org/research/index.php/whats-new/whatsnew-2014/147-misinterpreted-research
Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep. 2014;4:4133.

[73] Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H. Nicotine delivery to users from cigarettes and from different types of e-cigarettes. Psychopharmacology (Berl). 2017;234(5):773-779.

[74] Ibid

[75] Smets J, Baeyens F, Chaumont M, Adriaens K, Van Gucht D. When Less is More: Vaping Low-Nicotine vs. High-Nicotine E-Liquid is Compensated by Increased Wattage and Higher Liquid Consumption. Int J Environ Res Public Health. 2019;16(5).

National Academies of Sciences, Engineering and Medicine report published in 2018 that provided a detailed analysis of the emerging e-cigarettes landscape and the report commissioned by Public Health England that includes a larger analysis of the EU markets and policy, and TPD-compliant products.[76] We believe that, in this case, the Scientific Committee on Health, Environmental and Emerging Risks does not provide the Commission with a proper analysis of the e-cigarette landscape with regard to both risks and benefits that these products may provide in the larger tobacco products market.

[76] "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/ reports/2018/public-health-consequences-of-e-cigarettes.aspx and McNeill, A., Brose, L.S., Calder, R., Bauld, L., and Robson, D. (2020). Vaping in England: an evidence update including mental health and pregnancy, March 2020: a report commissioned by Public Health England. London: Public Health England.
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf