BAT's collated response to SCHEER's Preliminary Opinion on E-Cigarettes
26th October 2020

Abstract
The conclusions of SCHEER's Preliminary Opinion lack objectivity, omitting the 'most recent scientific and technical information available'.

The Opinion finds strong evidence for risks of long-term systemic effects on the cardiovascular system, moderate evidence for local irritative respiratory damage, and weak to moderate evidence of carcinogenicity of the respiratory tract. This is in contrast with the widespread available published scientific evidence. SCHEER have not considered positioning e-cigarette effects relative to cigarettes, which is supportive of their reduced risk profile, since they expose users and bystanders to reduced toxicant levels compared to smoking (1-2). There is little evidence nicotine is a risk factor for long-term cardiovascular disease (3-4). Studies have shown smokers who switch to e-cigarettes have significant improvements in their vascular function, with measurable effects in as early as 1 month (5). E-cigarette use has been shown to improve the outcome (harm reversal) from smoking in COPD (chronic obstructive pulmonary disease) patients (4). E-cigarettes have significantly lower levels of toxicants compared to cigarette smoke (6) and have been estimated to have cancer potencies less than 1% of tobacco smoke (7). Public health agencies such as the WHO's International Agency for Research on Cancer state nicotine does not cause cancer (8-14).

The Opinion finds moderate and weak to moderate evidence that second-hand vapour is a cause of local irritative damage to the respiratory tract and cancer and cardiovascular disease, respectively. Independent studies from medical and health associations, including the British Medical Association (15), conclude that emissions and second-hand vapour from e-cigarettes do not present any significant health risks to bystanders, with negligible levels of air pollutants compared to cigarette smoke (1,16-18). The excess life cancer risk from second-hand vaping has been estimated as 10,000 times lower than from second-hand smoking (19).

The Opinion claims strong evidence e-cigarettes are a gateway to smoking for young people. Comprehensive studies have criticised 'gateway' arguments made in relation to e-cigarettes and found no reliable evidence of a gateway effect (1,2,20).

While they are neither authorized nor marketed as cessation devices, several studies have shown e-cigarettes are effective in helping adult smokers quit smoking successfully (21-31), yet SCHEER infer the evidence available is weak. According to independent organisations, millions of smokers around the world have switched to using e-cigarettes (1,2,12,31-33). A recent study of 13,057 subjects from 28 EU countries found that compared with former smokers who never used e-cigarettes, daily e-cigarette users were 5 times more likely to have quit smoking (34). In the EU, 6 out of 10 people reportedly took up e-cigarettes to stop or reduce tobacco use (35).

Finally, the Opinion proposes there is strong evidence flavours contribute to the attractiveness of e-cigarettes. Numerous public health bodies, including WHO, have recognised the importance of flavours in vaping products to act as a satisfactory alternative to cigarette smoking (37-39). Cigarettes are arguably the 'most appealing, most addictive, and most toxic' nicotine product (40-42) available. If smokers switch to e-cigarettes, this would be in the interest of and benefit to public health (40,43,44). We respectfully request SCHEER to reconsider their conclusions, referring to evidence provided.

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Acknowledgements

BAT welcome the European Commission's efforts to understand the most recent scientific and technical information on e-cigarettes, as part of their review of the Tobacco Products Directive 2014/40/EU. However, we are disappointed with the Preliminary Opinion by SCHEER, which does not reflect the totality of the existing science on e-cigarettes. The SCHEER working group, supported by external experts, have omitted a significant body of literature on the role of e-cigarettes in providing public health benefits compared to continued cigarette smoking in an EU context. For example, the many peer-reviewed publications from industry scientists are noticeably absent.
We have therefore included our 53 peer-reviewed e-cigarettes publications including studies reporting on testing emissions, toxicological data, risk assessment of e-liquids flavours and ingredients, consumer and clinical studies and population modelling, for SCHEER's consideration. We have published our research in international peer-reviewed journals, choosing an open access option where possible, so there are no restrictions on

who can read our research, and links to all of these articles can be found in the library of www.bat-science.com, our dedicated science website, along with our @BAT_Sci twitter handle.

We are open and transparent about the scientific research that we do, also developing scientific collaborations with a wide range of groups. We actively participate in technical working groups, sit on steering committees and advisory panels, and also present our studies at international conferences, ranging from chemistry and toxicology to more specialist events on nicotine and tobacco science or aerosol science.
We cordially invite the SCHEER working group, external experts and other members of the SCHEER committee to visit our R&D site in Southampton, UK to learn more about the research that we conduct on e-cigarettes and also meet with our product developers and compliance teams to understand how we ensure our products are compliant with EU regulations. Since 2011, when we first developed our science exhibition centre, we have welcomed over 3500 visitors, all of whom wanted to learn more about the science behind e-cigarettes and other products. The groups have been diverse, ranging from science writers, mainstream media, journalists, academics, scientific collaborators, public health representative, regulators as well as consumer advocates.
E-cigarettes have a critical role for public health, for millions of adult EU smokers, as alternatives to smoking. We strongly encourage SCHEER to consider the important public health principle of tobacco harm reduction and to reconsider the conclusions in the draft Preliminary Opinion, referring to the literature attached.

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1.0 Summary

The summary could benefit from inclusion of references to support key statements using only published findings (P6,LN25) or links to the main body of text. Where data has been considered, the report relies heavily on US data (P7,LN11-12 and P7,LN12-13) without mention of TPD2. The US e-cigarette market, consumer attitudes and legislation are significantly different to that of the EU and therefore more EU-centric data should be considered.

E-cigarettes have lower emissions and toxicants compared to cigarettes, but harm reduction initiatives (1,2,3) are not addressed. Regulatory accepted *in vitro* techniques (4,5,6,7,8) exist and are routinely employed and should be used in the weight of evidence approach, rather than discounted in their entirety. Health effects focus predominately on CVD despite behavioral, environmental and genetic factors playing a significant role in other disease etiologies such as pulmonary disease (9,10). Moreover, CVD disease mechanisms in response to smoke are not well defined (11).
Divergence of e-cigarette technology is not considered, and all e-cigarettes format are considered equal in their risk. Misuse has a significant bearing on risk potential and again, is not considered (P13,LN12). New e-cigarette technologies (12) that could significantly impact absolute risk are not discussed.

Summary References

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2.1 Terms of Reference

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

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

In this respect we note that the Preliminary Opinion should but does not meaningfully address the potential positive health benefits for EU adult smokers using e-cigarettes as alternatives to smoking, ignoring the public health principle of tobacco harm reduction. Without taking these into account, SCHEER cannot adequately address the terms of reference, both in terms of addressing considerations relevant both at an individual level

and at a population level from a public health perspective (which must include smokers), as specifically required under the terms of reference, and in providing the required scientific analysis to assess the potential need for legislative amendments.

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

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

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

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

3.0 Scientific Opinion- Part 1

The Scientific Opinion section of the SCHEER Preliminary Opinion which summarizes the risk assessment and general product and product use evaluation for e-cigarettes exemplifies many issues that are common throughout the document and could influence the overall risk assessment outcome. Several main points of commentary are summarized

below and expanded on in subsequent comments on the Scientific Opinion (section 3) of the Opinion (P10,LN38).

The potential health benefits of e-cigarette use as a tobacco harm reduction alternative to smoking (1-7) are not meaningfully considered. The assessment should focus on the balance of risks between smoking and vaping and how this affects EU public health considering transitions between smokers, vapers and non-users (P10,LN47: “adverse health effects”; P18, Section 3).

Data derived from studies with either outdated products or only those available outside the EU are included. Risks are discussed in the report based on non-EU and pre-TPD legislation and are therefore not relevant in this context as these e-liquids/products (or resulting derivatives, constituents thereof) are not currently available/applicable in the EU (e.g. P12,LN1-5; P15,LN34; P16,LN21-25).
There is limited/incomplete or inconsistent data (design, methods, measurement) to support risk assessment conclusions. Crucial aspects of SCHEER’s risk assessment, such as choices of Point of Departure studies, exposure measurements and estimates, are not described nor explained in the report. Moreover, in some cases general conclusions about risk (including initiation, cessation) rely on a single, non-peer reviewed study that may or may not include all the information needed to support SCHEER’s overall findings/opinions (e.g. P14,LN20-30).

Confounding factors are not adequately discussed or considered in many of the referenced human behavior studies. Confounding factors such as race, intention to quit, nicotine dependence, etc., can vary across studies and study participants. These factors could have a profound effect on e-cigarette perception, use patterns and cessation outcomes (8).
The Scientific Opinion subsection on initiation (P16) fails to account for the variation in definitions used in many of the referenced studies on initiation of cigarette smoking. Collectively, these limitations invalidate the conclusion that the body of evidence is “strong” for e-cigarette use causing cigarette smoking initiation among youth.

Finally, the Opinion appears to apply different weights of evidence toward overall conclusions reached with respect to various endpoints (e.g. P15,LN5-17). Specifically, with respect to health effects, much of the evidence supporting potential links between e-cigarette use and health outcomes discussed in the Opinion are based on acute and/or *in vitro* observations. It is made clear in the report that long-term clinical studies are required to make any robust assessment of the health risks presented, as in the case of pulmonary disease. Nevertheless, the SCHEER concludes that similar acute or short-term *in vitro* observations provide “strong” evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system (P14-15).

Scientific Opinion – Part 1 References

1. McNeill A, Brose LS, Calder R, Bauld L, Robson D. Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England 2018. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf
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8. Lantz PM. Smoking on the rise among young adults: implications for research and policy. Tobacco control. 2003;12:i60-i70.

3.0 Scientific Opinion- Part 2

Data derived from studies with either outdated products or only those available outside the EU are included. Several risks discussed in the report are based on non-EU and pre-TPD publications, that are not relevant to e-liquids currently on the EU market. Concerns of TSNAs as impurities from nicotine in e-liquids are irrelevant as TPD requires ingredients to be of high purity; nicotine being of pharmaceutical grade purity and risks are thus comparable to those from nicotine replacement therapy (P16,LN22). While the Opinion reports that some devices in the US can potentially deliver as much nicotine as a cigarette, the evidence is from products containing higher nicotine levels than are allowed in the EU (P12,LN1-5). In contrast to stated evidence that “nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible

cigarettes", other studies show that nicotine uptake from e-cigarettes (up to 4% nicotine) is significantly below that of cigarettes (1-4).

There is limited/incomplete or inconsistent data (design, methods, measurement) to support risk assessment conclusions. Crucial aspects of SCHEER's risk assessment (choice of Point of Departure studies, exposure measurements and estimates) are not described. Some conclusions are based on a single, non-peer reviewed study that may not enable an objective opinion (P14,LN20-30). For example, conclusions on risks from second-hand aerosol exposure are based on a single study (P14,LN23), using unlikely extrapolations from exhaled breath rather than room air measurements, and assumes exposure scenarios that are unrealistically high compared to the SCHEER assumptions for the risk assessment for the main user. These conclusions could be supported by referral to the 2020 assessment from the UK Committee on Toxicity (5). Another example of limited support underpinning an opinion is the second-hand aerosol exposure assessment, ignoring published studies and relies on a single study that uses an inaccurate method to estimate room air concentrations and assumes highly unrealistic exposure scenarios (P12,LN29-40). While the potential second-hand exposure to non-users of e-cigarettes is likely, the exposure to non-users is several orders of magnitude lower than the exposure to smokers/vapers (more than the single order of magnitude found on P12,LN33). Numerous uncited publications have measured concentrations of secondhand smoke constituents and, with the general exceptions of PG, VG, and nicotine, however are comparable to background concentrations or not detectable (6-8). More examples of incomplete/flawed provision of information were noted with respect to study design, methods or measurements noted within some of the references.

Specifically, efforts to assess whether e-cigarette use causes cigarette smoking must consider "common liability" (predisposing factors of e-cigarette use are common to those of cigarette smoking). The common liability model, where inclination towards risk-taking and psychosocial processes can be factors, provides a parsimonious explanation of substance use and addiction co-occurrence (P16,LN52 - P17,LN32) (9-11).

Some of the systematic reviews in the Opinion do not support the gateway hypothesis (P18,LN35-39), despite SCHEER stating strong evidence. Causal inferences are not supported by the evidence and that youth using both e-cigarettes and cigarettes share a number of risk factors that increase their susceptibility to use either product (9) and are not adequately discussed. In particular, socio-demographic characteristics, willingness to take risks, and perception of comparative cigarette and e-cigarette risks and/or benefits all differentially influence cigarette smoking initiation (12).

Scientific Opinion – Part 2 References

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10. Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use among Non-Tobacco Users and Initiating Smoking of Combustible Cigarettes. 2019.
The review was sponsored by RAI Services (RAIS) Company and performed by Thera-Business. The review strictly adhered to AMSTAR 2 (score of "high," suggesting that it provides an accurate and comprehensive summary of the results of the available studies that address the question of interest) and PRISMA guidelines for systematic review methodological and reporting quality. This systematic review included a predefined protocol that was established prior to the conduct of the review and included the review question, a search strategy, inclusion/exclusion criteria, risk of bias assessment, a meta-analysis plan, and a plan for investigating heterogeneity. Additionally, the systematic review included a comprehensive search of MEDLINE, EMBASE, and PsycINFO using a reproducible search strategy. Unlike the Opinion, which arbitrarily excluded articles prior to 2015, our search dates were only restricted to exclude articles prior to 2007, because that

was when e-cigarettes were introduced to the mass market in the US. For transparency, the full search strategy as well as the list of excluded articles are included in the report. The quality of included studies was assessed with the Downs and Black checklist, one of the most rigorous instruments for evaluating observational studies. Finally, the review assessed the strength of evidence using a standardized method, the Agency for Healthcare Research and Quality (AHRQ) Evidence Based Practice (EPC) grading system, integrating an assessment of the contextual questions examined in the review.

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12. Lantz PM. Smoking on the rise among young adults: Implications for research and policy. Tobacco Control. 2003; 12:i60-i70.

3.0 Scientific Opinion- Part 3

The Scientific Opinion section of this Opinion detailing the risk assessment approach has significant deficits and fails to take into account key factors that could influence the overall risk assessment outcome.

Confounding Factors are not adequately discussed or considered in many of the referenced human use and behavior studies. The Opinion failed to discuss the importance of adjusting for factors between study groups within a given study that could influence the outcomes of interest. For example, different racial or ethnic groups could have different tobacco behaviours and perceptions that may influence cessation outcomes (1). Other confounding factors include intention to quit, which can vary across studies and study participants. These factors could have a profound effect on e-cigarette use patterns and cessation outcomes. Respondents with a higher motivation to quit are more likely to have a successful quit attempt. In a recently completed systematic review and meta-analysis on associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking, 101 studies were identified as investigating the association between e-cigarette use and abstinence from cigarette smoking. Among those studies, the majority (n= 77 studies, 76%) did not adjust for age, race, and sex (2). Thus, pooling a body of evidence with high heterogeneity among studies, many of which lack adjustments for confounding factors that influence the observed associations between e-cigarette use and cigarette smoking cessation outcomes, will inherently result in the evidence being graded as “weak.” This issue was also discussed in a systematic review that was included in the Opinion’s assessment of cessation (3).

The Opinion failed to account for the variation in definitions used in many of the referenced studies on initiation of cigarette smoking. The subsection on initiation in the Scientific Opinion section fails to account for the variation in definitions of initiation of cigarette smoking among the studies (P16, Section 2). In most cases, definitions of

initiation are more consistent with experimentation (e.g., “ever use”) than true initiation (4-5). Definitions for e-cigarette use and cigarette smoking initiation are inadequate for defining established behaviors. Collectively, these limitations invalidate the conclusion that the body of evidence is “strong” for e-cigarette use causing cigarette smoking initiation among youth. Comparator groups and e-cigarette use definitions are highly heterogeneous across the studies, limiting the overall synthesis of the evidence. For example, the comparator groups in the included randomized trials varied between studies, and included nicotine replacement therapy, nicotine-free e-cigarettes, and support/counselling (3,5-7).

In terms of e-cigarette use definitions, the Opinion failed to consider frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation (8).

Scientific Opinion – Part 3 References

1. Webb Hooper M, Kolar SK. Racial/ethnic differences in electronic cigarette use and reasons for use among current and former smokers: findings from a community-based sample. International journal of environmental research and public health. 2016 Oct;13(10):1009
2. Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use Among Cigarette Smokers and Changes in Continued Cigarette Smoking. 2020.
3. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic cigarettes for smoking cessation: A systematic review. Nicotine Tob Res. 2016;18(10):1926-36.
4. Glasser A, Abudayyeh H, Cantrell J, Niaura R. Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. Nicotine and Tobacco Research. 2019;21(10):1320-30.
5. Hajek P, Phillips-Waller A, Przulj D, Pesola F, Myers Smith K, Bisal N, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629-37.
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3.0 Scientific Opinion- Part 4

The Scientific Opinion section of this Opinion detailing the risk assessment approach has significant deficits and fails to take into account key factors that could influence the overall risk assessment outcome.

Incongruent Weight of Evidence Application: The Opinion appears to apply different weights of evidence toward overall conclusions reached with respect to various endpoints. Specifically, with respect to health effects, much of the evidence supporting potential links between e-cigarette use and health outcomes discussed in the Opinion are based on acute *in vitro* observations. Although it is made clear in the report that long-term studies are required to make any robust assessment of the health risks presented, the Opinion nevertheless concludes that similar acute or short-term *in vitro* observations provide strong evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system.

SCHEER treats cessation as a monolith, when in fact measures of cessation varied considerably and were often unique outcomes that should not be collectively grouped, e.g., 7-day point prevalence abstinence is a far different outcome than 12-month abstinence. The outcome measures should have been described and appropriately considered as unique measures (1). Failure to do so compromises the validity of the weight of evidence cited in the Opinion.

Additionally, the recent systematic review, which used a rigorous methodology to assess the weight of evidence for individual cessation measures, found that at present, there is insufficient evidence to support a conclusion that e-cigarette use is positively associated with continued cigarette smoking (2). The Opinion may have applied different weights of evidence for individual cessation measures, as observed in the recent systematic review (2). However, when combining cessation measures as a monolith, the weight of evidence should not have been “low” but rather “not possible.” The Opinion failed to consider frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation. The Opinion lacked the adequate justification for its evaluation of the strength of evidence as "weak" for cessation and "weak to moderate" for reduction. Given the variations in key parameters across the studies examining cigarette smoking cessation, heterogeneity was inevitable—and the studies should not have been synthesized as a single body of evidence.

Scientific Opinion – Part 4 References

1. Glasser A, Abudayyeh H, Cantrell J, Niaura R. Patterns of e-cigarette use among youth and young adults: review of the impact of e-cigarettes on cigarette smoking. Nicotine and Tobacco Research. 2019;21(10):1320-30.
2. Malas M, van der Tempel J, Schwartz R, Minichiello A, Lightfoot C, Noormohamed A, et al. Electronic cigarettes for smoking cessation: A systematic review. Nicotine Tob Res. 2016;18(10):1926-36.

4.0 Methodology

The weight of evidence (WOE) approach applied in the Opinion has several methodological limitations that undermine the transparency, reproducibility, comprehensiveness, and objectivity of this evidence synthesis.

Validity, an indicator of the extent to which a measurement process measures what it purports to measure, and reliability, the extent to which a measurement process yields the same results repeatedly, are critical considerations in an evidence synthesis (1,2), and the individual studies being interpreted. SCHEER's own WOE memorandum (2018) clearly states "For each line of evidence, the criteria of validity, reliability and relevance need to be applied and the overall quality has to be assessed" ((3) at P.4). However, without providing adequate and clear definitions or criteria, the Opinion's evidence synthesis is not transparent, not reproducible, potentially biased, and thus not generalizable.

The Opinion included outcomes that were not pre-defined in the Terms of Reference, e.g., reduction (Section 6.7). Furthermore, the Opinion did not disclose how specific outcome measures were identified, grouped, or discussed, which is problematic when certain pieces of evidence are collectively considered despite differing in outcome measures. For example, cessation studies were collectively presented despite heterogeneity among the comparators and abstinence duration (4). Consequently, the evidence synthesis is not objective, not comprehensive, and thus not generalizable.

The Opinion did not provide details on specific methods, measurements, and limitations that contributed to the upgrading or downgrading of the evidence. SCHEER's WOE memorandum (2018) suggests the use of other grading systems for quality of evidence assessment, including the GRADE approach (5). GRADE accounts for the risk of bias that can influence the estimate of effect, imprecision, and indirectness in study execution, application of results, and inconsistency and publication bias (3,5). The Opinion did not disclose details of its GRADE assessment, potentially rendering its quality of evidence conclusions unreliable and subjective. The application of an additional grading system would have strengthened this Opinion with transparency, reproducibility, reliability, and validity.

The Opinion's treatment and interpretations of systematic reviews are also inconsistent. Specifically, the Opinion reviewed several systematic reviews in Section 6.6, but there is no reference to a GRADE approach for the quality of evidence assessment. In Section 6.7, the Opinion specifies a GRADE rating for two systematic reviews; additionally, PRISMA guidelines (6) and AMSTAR 2 (7) would have rated the methodological and reporting quality of the reviews (8). This approach should have been applied throughout this evidence synthesis.

Finally, the methodological approach of the Opinion lacked a transparent, pre-defined analytic plan, critical study details (e.g., the number of studies from the search, the number of included studies), and study inclusion/exclusion criteria. The approach also lacked a clearly defined process for generating themes and how other methods (e.g., search strategy, analysis plan, how evidence would be presented) were executed (9). A

panel of key expert stakeholders in the evidence outcomes should have been formed to formalize a set of themes for systematic synthesis and the application of other research methods; for example, a consensus development using techniques such as the Delphi method (10). As a consequence, key fundamental research papers were omitted, including EU studies.

Given the many methodological deficiencies in the Opinion, the conclusions cannot be accepted with any confidence and refer SCHEER to the attached literature.

Methodology References

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The review was sponsored by RAI Services (RAIS) Company and performed by Thera-Business. The review strictly adhered to AMSTAR 2 (score of “high,” suggesting that it provides an accurate and comprehensive summary of the results of the available studies that address the question of interest) and PRISMA guidelines to evaluate the methodological and reporting quality of systematic reviews investigating to evaluate systematic reviews that compared the impact of e-cigarettes (nicotine-free and/or nicotine-containing) with any relevant comparator (i.e., articles were not restricted based on the comparator) on combustible cigarette smoking behaviors in youth, young adults, and/or adults. The systematic review protocol followed PRISMA guidelines for best practice in systematic reviews and was prospectively registered with the PROSPERO registry for systematic reviews (CRD42018078252). The protocol can be found at: https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=78252. There were no significant deviations from the protocol. Additionally, the systematic review included a

comprehensive search of MEDLINE, EMBASE, and PsycINFO using a reproducible search strategy. Unlike the Opinion, which arbitrarily excluded articles prior to 2015, our search dates were only restricted to exclude articles prior to 2007, because that was when e-cigarettes were introduced to the mass market in the US. For transparency, the full search strategy as well as the list of excluded articles were fully provided in a final report. The methodological quality of previously published systematic reviews was assessed with the AMSTAR 2 tool and. Finally, the reporting quality of previously published systematic reviews was assessed with the PRISMA statement.

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5.0 Terminology

SCHEER applied a broad definition of e-cigarette use in its evidence synthesis that fails to take into account frequency of e-cigarette use or e-cigarette use patterns. Therefore, it is impossible to draw conclusions on a causal association between e-cigarette use and cigarette smoking initiation or cessation. Simply measuring “ever” or “current” use is inadequate—particularly in adolescents—as these measures are heterogeneous categories incorporating experimental, occasional, and regular use (1, 2).

The strongest evidence for evaluating cigarette smoking initiation is provided by studies of regular e-cigarette use transitioning to regular cigarette smoking. Conversely, the weakest evidence is provided by studies of use that are in line with e-cigarette and cigarette experimentation, which may or may not contribute to established product use behaviors.
Looking at the frequencies of e-cigarette use applied by studies included in a recently completed systematic review on the potential associations between e-cigarette use among nonusers of tobacco and initiation of cigarette smoking, no studies evaluated regular e-cigarette use transitioning to regular cigarette smoking. Furthermore, only one of 48 studies evaluated the association between regular e-cigarette use and any measure of cigarette smoking initiation—specifically, weekly/daily e-cigarette use to “ever having smoked a whole cigarette” (3).

The recent systematic review also stratified outcome measures by “initiation” (any cigarette use) and “initiation and progression to regular cigarette smoking” (daily, weekly, or current established cigarette use). Among the 44 initiation studies, “ever” use was the most common measure for both e-cigarette use (36 studies) and cigarette use (34 studies); among the 10 studies evaluating cigarette smoking progression, “ever” e-cigarette use again was the most commonly applied definition of e-cigarette use (5 studies) (3). (The sum of e-cigarette use measures may not equal the overall number of studies due to the application of multiple measures in some studies).
Similarly, the strongest evidence for evaluating cigarette smoking cessation is provided by studies of regular e-cigarette use transitioning to sustained and prolonged smoking abstinence. Conversely, the weakest evidence is provided by studies of use that are in line with e-cigarette

experimentation, which is unlikely to contribute to smoking cessation among regular cigarette smokers.

A second systematic review on associations between e-cigarette use among cigarette smokers and changes in continued smoking identified 101 studies evaluating cigarette use and abstinence/quitting cigarette smoking, of which 38 studies evaluated regular e-cigarette use (4). Current (any past 30-day) e-cigarette use was the definition used in 50 studies, while “ever” e-cigarette use was used in 23 studies. (The sum of e-cigarette use measures may not equal the overall number of studies due to the application of multiple measures in some studies). Furthermore, the second systematic review identified 81 studies that examined e-cigarette use and change in cigarette smoking quantity/frequency (reduction), of which 38 studies evaluated regular e-cigarette use. Current e-cigarette use was the definition used in 38 studies, while “ever” e-cigarette use was used in 16 studies (4). (The sum of e-cigarette use measures may not equal the overall number of studies, due to the application of multiple measures in some studies).

In conclusion, the determination of causal associations between e-cigarette use and cigarette smoking initiation and cessation must be guided by the highest level of evidence, which would include measures of regular use for both e-cigarettes and cigarettes (1, 2).

Terminology References

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3.Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use among Non-Tobacco Users and Initiating Smoking of Combustible Cigarettes. 2019.
The review was sponsored by RAI Services (RAIS) Company and performed by Thera-Business. The review strictly adhered to AMSTAR 2 (score of “high,” suggesting that it provides an accurate and comprehensive summary of the results of the available studies that address the question of interest) and PRISMA guidelines for systematic review methodological and reporting quality. This systematic review included a predefined protocol that was established prior to the conduct of the review and included the review question, a search strategy, inclusion/exclusion criteria, risk of bias assessment, a meta-analysis plan, and a plan for investigating heterogeneity. Additionally, the systematic review included a comprehensive search of MEDLINE, EMBASE, and PsycINFO using a reproducible search strategy. Unlike the Opinion, which arbitrarily excluded articles prior to 2015, our search dates were only restricted to exclude articles prior to 2007, because that was when e-cigarettes were introduced to the mass market in the US. For transparency, the full search strategy as well as the list of excluded articles are included in the report. The quality of included studies was assessed with the Downs and Black checklist, one of the most rigorous instruments for evaluating observational studies. Finally, the review assessed the strength of evidence using a standardized method, the Agency for Healthcare Research and Quality (AHRQ) Evidence Based Practice (EPC) grading system, integrating an assessment of the contextual questions examined in the review.

4.Kim MM, Steffensen I, Miguel RTD, Carlone J, Curtin GM. A Systematic Review Investigating Associations between E-Cigarette Use Among Cigarette Smokers and Changes in Continued Cigarette Smoking. 2020.
The review was sponsored by RAI Services (RAIS) Company and performed by Thera-Business. The review strictly adhered to AMSTAR 2 (score of "high," suggesting that it provides an accurate and comprehensive summary of the results of the available studies that address the question of interest) and PRISMA guidelines for systematic review methodological and reporting quality. This systematic review included a predefined protocol that was established prior to the conduct of the review and included the review question, a search strategy, inclusion/exclusion criteria, risk of bias assessment, a meta-analysis plan, and a plan for investigating heterogeneity. Additionally, the systematic review included a comprehensive search of MEDLINE, EMBASE, and PsycINFO using a reproducible search strategy. Unlike the Opinion, which arbitrarily excluded articles prior to 2015, our search dates were only restricted to exclude articles prior to 2007, because that was when e-cigarettes were introduced to the mass market in the US. For transparency, the full search strategy as well as the list of excluded articles are included in the report. The quality of included studies was assessed with the Downs and Black checklist, one of the most rigorous instruments for evaluating observational studies. Finally, the review assessed the strength of evidence using a standardized method, the Agency for Healthcare Research and Quality (AHRQ) Evidence Based Practice (EPC) grading system, integrating an assessment of the contextual questions examined in the review.

6.4 Chemical Ingredients in e-liquids

SCHEER's approach to e-liquid ingredients has limitations, provides inappropriate information and does not advance sound scientific principles, for example Table 2 (P24).

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

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

PG has been evaluated in multiple toxicological studies, including oral and inhalation routes, demonstrating a low potential to manifest toxicity. The EFSA Panel on Food Additives and Nutrient Sources added to Food reaffirmed an ADI of 25 mg/kg bw/day (1). Approvals by regulatory bodies for use in food for human consumption do not include evaluation for potential respiratory toxicity when used as a tobacco product ingredient. Such approvals for use in food do, however, demonstrate that qualified scientists have concluded that PG is of low inherent toxicity. EFSA specifically concluded that acute toxicity was low based on the review of numerous acute toxicity studies, with LD_{50} values ranging from 18,350-33,500 mg/kg bw across mice, rats, rabbits and guinea pigs (1). These data are not consistent with an H302 CLP classification (harmful if swallowed).

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

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

In 2018, Dalton et al. assessed the potential human toxicity of acute PG inhalation exposure in 10 men and 10 women exposed for 4 hours at 100 mg/m^3 and 30 minutes at 200 mg/m^3 to PG aerosols (5). Objective measures evaluated in this study included ocular irritation via eye blink task and eye photography, as well as pulmonary function via spirometry. Subjective measures included health symptoms ratings, irritation and dryness ratings of eyes, nose, throat and mouth. No respiratory or ocular effects were observed, leading the authors to conclude that, at the concentrations tested, PG does not affect respiratory function or produce ocular irritation (5). Overall, these data are not consistent with an H319 CLP classification (Eye Irrit 2) or respiratory irritation hazard for PG.

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

6.4 Chemical ingredients in e-liquids References

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

In SCHEER's Preliminary Opinion, the approach to risk assessment does not take into account the public health principle of tobacco harm reduction and therefore results in an outcome that is inconsistent with the available evidence.

(LN37-38) states that "chemicals present in the aerosols are responsible for the health effects"; however, SCHEER fail to acknowledge the overall reductions in chemicals present (toxicants and carcinogens) in e-cigarette aerosols compared to cigarettes that has led to widespread agreement amongst experts and public health authorities that vaping is less risky than smoking (1-4).

The Opinion looks to identify whether there is any residual risk with e-cigarettes and does not look at a balance of risks. It is already widely accepted that vaping is not risk-free (1-3), so a SCHEER report concluding only that will not be helpful. Data in the EU show regular e-cigarette use by never smokers remains very rare (3,5-11) and similar to that of licensed nicotine products (12). Using e-cigarettes as a way of quitting smoking is actively encouraged in several EU Member States (3,13-15). This section should therefore, in addition to characterising the residual risk from vaping, investigate the risk reduction to the user when switching from smoking to vaping. The relevance of this to public health in the EU should then be put into context by considering transitions between smokers, vapers and non-users.

(LN 44-45): SCHEER suggest they consider epidemiological or clinical trials on e-cigarettes to inform their assessment of health risk, yet their conclusion is at odds with the current evidence. A number of studies have shown the reduction in exposure biomarkers in smokers when switching to e-cigarettes (16-17).

(LN47-48): with regards to youth vaping, sales to minors are already prohibited and a review of the science assessing enforcement efficacy and various potential new measures to reduce youth access and use would be relevant to inform the Commission's policy development thinking.

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

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

6.5 Assessment of Health Risks References

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20. General Product Safety Directive (GPSD) (2001/95/EC) Directive 2001/95/EC of the European Parliament and of the Council.

6.5.1. Consumer Behaviour Related to Exposure Assessment

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

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

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

Second, the comparison of e-cigarette and cigarette smoking is not consistently applied. Although the Opinion discusses e-cigarette users compared to cigarette smokers in terms of e-cigarette users taking longer puffs and having longer use sessions compared to cigarette smokers, within the section on frequency of e-cigarette use in youth, there are no data presented regarding cigarette smoking frequency. The implication of the frequency section appears to be that e-cigarette use is rising in youth and young adults. However, SCHEER do not address similar trends for cigarette use among youth, where a decrease in prevalence is observed (7). Considering consumer trends for both products is important as the inverse relationship in use frequency between e-cigarettes and cigarettes could potentially mean that respondents predisposed to smoking cigarettes are being redirected to a potentially less harmful product. Estimates and assumptions used to model potential exposures must likewise consider cigarette trends to account for the risk and benefit balance between e-cigarettes and cigarettes.

In conclusion, SCHEER fail to adequately assess the WoE among studies with inconsistent design, methods, unvalidated topography equipment and measurements. SCHEER inadequately synthesises the body of evidence with a weight of “moderate to strong,” despite the methodology applied for appraising the WoE allowing only for a maximum grade of “moderate” for evidence of low consistency. Additionally, inconsistently referencing cigarette use behaviors calls into question the assumptions and estimates that

could be used in subsequent assessments of exposures. We therefore request SCHEER to re-evaluate their approach.

6.5.1. Consumer Behavior Related to Exposure Assessment References

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6.5.2 Exposure Assessment- Part 1

We respectfully request SCHEER to correct and amend the following:

P29,LN2-7: text appears to be standalone – it is context.

P29,LN10-16: clarification of particle concentration from e-cigarettes required as stated as 4x 10^9 and “of the order of 10^6 to 10^7 particles/cm^3.

P29,LN37-42: data reported in the publication of Williams et al. (1) is based on a single product type tested in 2012/13 and as such is highly unlikely to represent more modern e-cigarette designs. More recent publications quantifying metals in e-cigarette aerosol have demonstrated metals below limits of detection, quantification and below or not statistically different to background levels and should therefore be included in the weight of evidence P30,L4-30, Margham et al. (2), Flora et al. (3), Farsalinos et al. (4), Farsalinos and Rodu (5), Tayyarah and Long (6). Data from Williams et al. (7) are relevant to P36,LN23-56.

P29,LN9: the term ultrafine particles may lead to misunderstanding as they should be viewed as ultrafine droplets, explained by the short lifetime as stated in L13.

Section 6.5.2.2 Data from early generation e-cigs are over-represented in comparison to their current level of use by consumers.

Section 6.5.2.3 depends heavily upon the data of Visser et al. The cited RIVM reports do not seem to address the potential background chemical contribution to levels reported in aerosols (2) and may overestimate results.

P30,LN24 & P37,LN6: ethylene glycol is listed as a solvent carrier, however, this is not listed as an ingredient in e-liquids within the EU, as stated in Appendix 2 of the report.

P30,LN25 & P37,LN6-7: TSNAs are listed as an impurity of nicotine, whilst P36,LN5-6 refers to a publication showing no TSNAs were detected, additional publications have also reported on the presence of TSNAs in e-liquids (3,6). TPD requires the use of high purity ingredients with various national standards (8,9) clarifying this means the use of pharmaceutical grade purity.

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

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

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

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

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

6.5.2 Exposure Assessment- Part 1 References

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6.5.2 Exposure Assessment- Part 2

We respectfully request SCHEER to correct and amend the following:

P32,Table 3: data from Visser et al. (1,2) covering up to 17 products, are representative of those available at the time and therefore may not reflect more modern designs of products.

P33,LN14: nicotine transfer to e-aerosol is impacted by PG/VG composition and device power Kosmider et al. (3).

P33,LN26-27: data for glycerol and glycols in aerosol have been published (1).

P35,Table 4 lists data from Goniewicz et al., 2014, however there are two entries for Goniewicz et al., published in 2014, within the references section of the report.

P35,LN13-15: clarification should be added to state that 9 of the 11 VOCs tested for were not found in the aerosol of the 12 products tested. Data on selected VOCs have be published (4,5).

P36,LN5-8: TSNA data in Goniewicz et al. (7) have not been replicated and relate to products that are no longer commercially available, additional publication listed in section 6.5.2 (4-6).

Visser et al. (1) report summarizes “A small proportion of liquids contain diethylene glycol, benzene, toluene or TSNAs, but those substances were not demonstrably present in the great majority of liquids.” Thus the substances of primary interest regarding e-cigarette exposure are formaldehyde, acetaldehyde, acrolein and trace metals in the aerosol.
P37,LN9-10: use of maximum values of compounds as reported by Visser et al., (1,2) does not represent concentrations that would be measured from more modern designs of e-cigarettes.

P38,LN15-22: second-hand exposure risk assessment uses maximum values reported by Visser et al. (8), based on popular products tested in the research by Visser et al. (2) and is therefore of limited relevance to current products. The data are based on 17 volunteers with considerable variation in average exhaled volume ranging from 33 to 1528 mL, noted as not representative for normal exhalation or breathing volumes (9).

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

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

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

6.5.2 Exposure Assessment- Part 2 References

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6.5.3. Hazard Identification of Most Relevant Compounds- Part 1

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

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

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

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

For any statement, the hazard identification aspects should be made explicit, e.g. the importance of GRAS and food additive status provides assurance of low potential systemic hazards (P41,LN26). For those same compounds that have adequate oral data but are

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

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

P41,LN51-57: recite speculative notions and hypotheses regarding menthol that are extracted from SCENIHR (2016) who cite a 2011 US-FDA TPSAC and a 2013 FDA preliminary menthol report (4,5) as their basis. SCHEER, however, neglects to cite major FDA conclusions that soundly refute these speculative mechanisms, i.e., "menthol in cigarettes is likely not associated with increased or decreased levels of biomarkers of exposure" and "menthol in cigarettes is not associated with an increase in disease risk to the user compared to nonmenthol cigarette smokers" (5). There is no factual evidence to support the speculation that the physiological properties of menthol result in greater exposures or consequent disease or addiction risks for e-cigarette users, but there are numerous publications refuting each aspect of the hypothesis in cigarettes: studies of exposure biomarkers (6-9), disease epidemiology (10-12), or addiction/dependence (13).

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

6.5.3 Hazard Identification of Most Relevant Compounds- Part 1 References

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6.5.3. Hazard Identification of Most Relevant Compounds- Part 2

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

Glycerol is used in many foods, cosmetics and drug products, including a number of bronchioinhalants up to 5% of the formulation (1). In a comprehensive review, glycerol was determined to not be a dermal or ocular irritant (2,3). Additionally, glycerol is of low acute oral toxicity and an EFSA Panel considered that local irritating effects in the GI tract reported in some gavage studies in rat and dogs were likely caused by hygroscopic and osmotic effects of the large bolus doses administered (4). Glycerol is also a natural component of the human body, comprising ~1% of body weight. It is readily metabolized to CO2 and glucose, which is subsequently incorporated as liver glycogen through normal metabolic processes (4). The combined influences of the large quantities of endogenous glycerol and its very rapid metabolism and clearance have been shown to render measurement of biomarkers of stable isotope-labeled glycerol delivered from e-cigarette use difficult or impossible to quantify (5). These diverse approvals for use in foods, cosmetics and pharmaceuticals along with its rapid disposition and elimination are all consistent with a very low order of toxicity and none are consistent with an expectation it could have any meaningful irritation of eyes, respiratory tract or GI mucosa.

PG has broad uses in pharmaceutical and consumer products, and as an inactive ingredient in drug formulations. It is used to absorb extra water and maintain moisture in certain medicines, cosmetics and food products. It is a solvent for food colors and flavors and is used as a pharmaceutical excipient in several dosage forms, including as a co-solvent in inhaled aerosols (10-25%) (1,6). The EFSA Panel on Food Additives and Nutrient Sources added to Food reaffirmed an ADI of 25 mg/kg bw/day and indicated that PG was of low irritant potency (6). In 2018, Dalton et al. assessed the potential human toxicity of acute PG inhalation exposure in 10 men and 10 women exposed for 4 hours at 100 mg/m^3 and 30 minutes at 200 mg/m^3 to PG aerosols (7). Objective measures evaluated included ocular irritation via eye blink task and eye photography and pulmonary function via spirometry. Subjective measures included health symptoms ratings, irritation and dryness ratings of eyes, nose, throat and mouth. No respiratory or ocular effects were observed, leading the authors to conclude that, at concentrations tested, PG does not affect respiratory function or produce ocular irritation (7).

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

6.5.3 Hazard Identification of Most Relevant Compounds- Part 2 References

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3. Cosmetic Ingredient Review Expert Panel. Safety Assessment of Glycerin as Used in Cosmetics. 2015. Accessed via https://online.personalcarecouncil.org/ctfa-static/online/lists/cir-pdfs/FR679.pdf.
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7. Dalton P, Soreth B, Maute C, Novaleski C, Banton M. Lack of respiratory and ocular effects following acute propylene glycol exposure in healthy humans. Inhalation Toxicology. 2018; 30(3):124-132.

6.5.4. Human Evidence for Health Impacts of Electronic Cigarettes- Part 1
(* see also Supporting Evidence for Section 6.5.4. Human Evidence of Health Impacts of Electronic Cigarettes (CVD)- Part 1)

This section on the potential for e-cigarettes to cause cardiovascular disease indicates throughout that more evidence is needed and more specifically, that long-term studies are required. However, short-term and acute effect studies, along with hypothetical speculation, are being used to highlight long-term effects such as endothelial dysfunction, oxidative stress, hypertension and cardiac arrhythmias. In addition, these studies highlight their own limitations, for instance Moheimani et al. (1) could only rely on self-reporting of subjects who were asked not to smoke and indicated the unreliability of data collected on product use. Of note, as most of the people switching to e-cigarettes from smoking combustible cigarettes one must also take into consideration that effects on cardio-vascular health could be a consequence of other underlying diseases (2).

In addition, this section fails to put these potential effects of e-cigarettes in context with combustible cigarette use. There have been reports of improvement in endothelial function and vascular stiffness within one month of switching from smoking combustible cigarettes to e-cigarettes (3,4). Additionally, there are studies that report significant reduction in blood pressure with switching from smoking combustible cigarettes to e-cigarettes (5), while others report improvement in pulse wave velocity and reduction in malondialdehyde, an indicator of oxidative stress (6).

Some of the references are outdated (e.g. Chen 2013 (7)), which raises concerns over this information's relevance with regards to current products on the market.

Some statements are not referenced (e.g. P48,LN30-31 "Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells"), incorrect references are used (P48: Farsalinos et al 2014 (8)) and some references do not support the claims being made (P48: Franzen et al 2018 (9)).

Generally, this is not a balanced review of the literature and, in fact for the Benowitz and Burbank 2016 reference (10), only a table of potential diseases associated with nicotine use is included. Yet, this paper should be central to this section as it attempts to show from the current literature where e-cigarettes are in terms of potential cardiovascular disease risk in comparison to smoking combustible cigarettes. It also states: "While people with established CVD might incur some increased risk from e-cigarette use, the risk is certainly much less than that of smoking. If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be substantially reduced and there would likely be a substantial net benefit for cardiovascular health" (10). This aligns with other publications which indicate that although e-cigarettes are not harmless, in terms of the risk continuum they are likely to be less harmful than combustible cigarettes (11,12,13).

Overall, the evidence suggests that chemicals other than nicotine are responsible for the elevated risks of myocardial infarction and stroke in smokers. The beneficial epidemiological CVD risk outcomes of smoking cessation are well known and the use of NRT as a cessation aid does not increase CVD. Therefore, it is unproven that nicotine increases CVD risk, and many regulatory agencies such as FDA and PHE state that it is the toxicants from combusted tobacco, and not nicotine, which is causative of smoking-related diseases (14,15).

6.5.4 Human evidence for health impacts of electronic cigarette – Part 1 References

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6.5.4. Human Evidence for Health Impacts of Electronic Cigarettes- Part 2

The FDA recently published the Technical Product Lead (TPL) assessment of an MRTP application. In the TPL summary it classed certain HPHCs according to disease relevant toxicity. In terms of cardiovascular toxicity, Acrolein, benzene and 1,3-butadiene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders will be exposed to with glo relative to cigarette smoke.

Similarly, in terms of respiratory toxicity, Acrolein, acrylonitriles, 1-aminonapthalene and toluene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders are exposed to with glo relative to cigarette smoke.

Finally, for reproductive toxicity, benzene, 1,3-butadiene, carbon monoxide, ethylene oxide, nicotine and toluene were cited as relevant. A review of the levels of these chemicals and their subsequent levels of biomarker of exposure (Section 4) shows there is a clear reduction in the levels of these chemicals that users and bystanders are exposed to with glo relative to cigarette smoke.

This Opinion is limited and fails to incorporate a number of publications that indicate that e-cigarettes are not entirely without harmful effects but are likely to be less harmful than combustible cigarettes (2-5).

The Opinion points to strong evidence for e-cigarettes causing long-term systemic effects on the cardiovascular system. However, as is made clear in the Opinion, long-term studies

are required to verify this while the report bases its findings mainly on studies on acute effects of e-cigarettes to support this position.

Some statements are not referenced (e.g. P48,LN30-31 “Recent findings demonstrate that volatile liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells”), incorrect references are used (P48: Farsalinos et al 2014 (6) and some references do not support the claims being made (P48: Franzen et al 2018 (7)).

Potential lung disease effects are largely attributed to acute in vitro studies, many of which are quite old and have little relevance to modern e-cigarettes. It relies a lot on certain in vitro studies, while ignoring other (e.g. 8, 9). Potential links between observations in in vitro studies and cancer risk are also mentioned, while acknowledging that clinical evidence is lacking.

The section on ENDS use and effects in the oral cavity contains no citations.

6.5.4 Human Evidence for Health Impacts of Electronic Cigarettes – Part 2- References

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6.5.4. Human Evidence for Health Impacts of Electronic Cigarettes- Part 3

P47,LN13-25: Acute mouth/throat irritation and cough are mentioned in this report, citing studies that specifically looked at switching from cigarettes to e-cigarettes (1,2). Palamidas also looked at the effects of vaping nicotine-free e-liquids in by non-smokers (2). In both studies, the e-cigarette used were early generation devices. In the Polosa study (1), these effects were greatly diminished by the end of the study (week 24). Palamidas actually notes that their study involved 10 minutes vaping in group of vaping-naive individuals, and the effects could be mitigated by experienced vapers. He also reflected that later-generation devices may have different effects.

The lung disease section draws on a mixture of individual studies and review articles. Many of these references conclude that further evidence is needed on long-term effects of e-cigarette usage, and this is mentioned in the report section itself. However, some of the statements do not echo these limitations.

For example, P49,LN6 states e-cigarette studies demonstrate that e-cig use triggers increased airflow resistance, citing an old reference (3), and that paper only hypothesises this potential health effect from flavouring compounds at the time that had links to this endpoint. P49,LN10 describes increased mucin production in e-cig users, but the referenced study (4) does not have clear information on product use (overall product consumption and whether these were solus/dual users).
P49,LN13 links e-cig use to asthma in adolescents, but the cited reference noted there are no long-term studies to confirm either way (5).
P49,LN15 mentions potential links between observed perturbations in apoptosis/necrosis, inflammatory cytokine expression, and ROS generation by e-cigarettes/e-liquids in in vitro studies and cancer, while acknowledging clinical evidence is lacking. Our in vitro studies on Vype ePen in MucilAir did not indicate many of these pathways are perturbed at the gene level and cytokine release is low, and significantly lower than following cigarette smoke exposure (6,7). Objective comparisons to cigarette smoke exposure are absent from this section.

The section on other health effects begins (P49,LN24) with an investigation of the link between e-cig use and head and neck cancer. The only source cited was a review (8) covering only 18 out of 359 studies. Studies selected were mainly in vitro, and the authors concluded that the evidence to date is unclear and longer term studies and more data are needed to make any strong conclusion.
P50,LN5-15 on mental health effects relies solely on one recently published cross-sectional study (9), in which the direction of association could not be established due to study design.
The section on second-hand exposure effects is very weak on evidence, and P52,LN1-2 even states that ‘to date data on the long-term consequences of passive smoking of electronic cigarettes on human health are lacking’. Many studies on passive cigarette

smoking are cited, but the relevance of these to e-cigarette second-hand exposure is highly questionable.

The section on health effects related to second-hand exposure to aerosol from electronic cigarettes is extremely light on evidence. It cites a study that is currently ongoing but with no published data (10), refers to studies on passive cigarette smoking CVD effects (P51,LN44-52) that are not relevant to e-cigarette second-hand exposures, and states that nothing substantial has been reported for e-cigarette equivalent exposures.
Third-hand smoke exposure is also mentioned in the context of e-cigarette equivalent exposure, but again relevance is lacking, and there are no data on long term effects in any case.

6.5.4 Human Evidence for Health Impacts of Electronic Cigarettes –Part 3 References

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6.5.4. Human Evidence for Health Impacts of Electronic Cigarettes- Part 4

P53,LN42-52: Safety Gate searches on faulty power adaptors (typically used for all Li-ion rechargeable battery powered devices) using key-word 'power adaptor', 'USB charger', 'USB power adaptor' yielded n= 40, 148 and 15 respectively (n total 203). When searching for 'battery' recalls there are 1147 results. Which puts the quoted e-cigarette findings (incidence n = 10) as very low and into context for risk levels due to 'Electrical appliances and equipment', where "Hoverboard" product recalls have 56 entries over the same period.

P53,LN53-56: the quoted recalls appear to relate to adaptor failures and not necessarily e-cigarette faults; adaptor failures are general risk for all electronic appliances (see previous comment on adaptor failures).

P54,LN1- 4: the remaining one-off e-cigarette battery failure, although a severe occurrence, is still very low when compared to the Safety Gate searches on power adaptor type (n = 203) and battery recalls (n = 1147) and other lithium rechargeable products (hoverboards n = 56).

P54,LN5-8: the LVD (2014/35/EU) covers health and safety risks on electrical equipment operating with an input or output voltage of between 50 and 1000 V for AC, 75 and 1500 V for DC – e-cigarettes as products are typically 5V DC and fall outside LVD compliance requirements. Accepted that power adaptors would be covered under LVD, EMC, RoHS and eco-design requirements for all electronic products (not just e-cigarettes). E-cigarette products are covered directly by the CE marking directives of EMC (2014/30/EU) and RoHS (2011/65/EU) and then by aspects of the General Product Safety Directive (GPSD) (2001/95/EC). GPSD sets out safety requirements for all consumer products being placed on the European market (and allows the use of adjacent standards, such as within the LVD safety standards, to control failure modes and risks), but is not a CE marking Directive.

6.5.4 Human Evidence for Health Impacts of Electronic Cigarettes – Part 4 References

1. Directive 2014/30/EU of the European Parliament and of the Council relating to Electromagnetic Compatibility (EMC) (2014/30/EU)
2. Directive 2011/65/EU of the European Parliament and of the Council on the Restriction Of the use of certain Hazardous Substances in electrical and electronic equipment (RoHS) (2011/65/EU)
3. Directive 2001/95/EC of the European Parliament and of the Council on General Product Safety Directive (GPSD) (2001/95/EC)

6.5.5. Risk Assessment- Part 1

Prioritisation (P55,LN27-53) is meant to be based on sections 6.5.3 and 6.5.4, yet the decision (P55,LN52) to focus only on the organic substances in Table 5 is not aligned with the discussions in either of those sections, see e.g. P37,LN5-8.

In the risk assessment, the report relies solely on the maximum levels measured in aerosol from a single, non-peer reviewed, study using pre-TPD2 products (1,2) with little relevance to current products in the EU. This study is does not appear to address the potential background contribution to aerosol levels, the importance of which has been published on (3,4), and thus very likely overestimates results.

P55,LN17-19 indicate how crucial choices of PoD studies and exposure estimates are, yet reasons for the choices made are not provided. Instead, in 6.5.5.3, the report refers to a single, non-peer reviewed study (1,2). This is an inappropriate study on several counts. Firstly, the exposure scenarios used do not correlate well with those described in 6.5.1 of the SCHEER report. Secondly, it relies on a single, unpublished, pre-TPD2 survey of 456 users, ignoring the wealth of data available in the literature, some of which is described in section 6.5.2.1, but not used in the risk assessment. Thirdly, it estimates peak alveolar doses for local effects. Literature quoted in the SCHEER report indicate most e-liquid aerosol is deposited in the tracheobroncheal tract. Additionally, animal studies and human experience show the main local effect is mild upper respiratory tract irritation that requires sustained exposure before manifestation. Average concentrations over time in the upper respiratory tract are thus the most relevant exposure measure. Furthermore, the assumed low absorption rate of 30% results in cumulatively increased alveolar estimates and is in contrast to data available on the main components, nicotine, PG and glycerol, and the study authors statements on aldehydes (p.55 in Visser et al 2016 (5)), all indicating rapid absorption from the respiratory tract.

Overall the study significantly overestimates exposure, which leads to the conclusion (P58,LN7-8) that “Carcinogenic effects can be expected to occur due to exposures to nitrosamines and formaldehyde.” No attempt is made to contextualise this theoretical approach with published clinical biomarker data. In long term use of electronic cigarettes, biomarkers for nicotine, TSNAs and VOCs were compared to that of NRT, demonstrating TSNAs and VOC exposure was no different, or lower than, that of NRT use (6). This is consistent with the large body of biomarker work, not referred to at all in the SCHEER report, that consistently shows rapid reductions in exposures to TSNAs and VOCs when switching from smoking to electronic cigarettes[7-13]. Based on clinical data, carcinogenicity risks from these compounds is thus likely to be low, potentially comparable to that from long term NRT use.
The supposed risk of local damage from exposure to polyols, aldehydes and nicotine (P60,LN55-P61,LN13) is partially based on the false premises that these substances are all irritants. By far the biggest contributors to the aerosol are propylene glycol and glycerol, both of which have been reviewed by several expert groups and not identified as irritants (14-18). They are used as solvents in (inhalation) medicinal and cosmetic applications precisely because of their tissue compatible nature. The “line of evidence” that cohort studies consistently demonstrate mouth and throat irritation dissipates over time, is contrary to the suggestion of cumulative irritation leading to damage over time. The flaws in the study (2) leading to the overestimation of exposures of nicotine (P61,LN7-9) and aldehydes (LN10-13) have been described above.

6.5.5 Risk Assessment – Part 1 References

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6.5.5. Risk Assessment- Part 2

The discussion favouring the use of MoE (6.5.5.2) is based on the false premises that data from a more continuous exposure scenario is not applicable to e-cigarette use.

Applicability depends on the toxic effect of concern. Both animal studies and human data suggest an absence of acute effects mediated by peak exposure. The uncertainty is around potential effects from sustained exposures. For this, average exposure concentrations over time, and therewith HBGV and animal inhalation set ups, are appropriate. Additionally, HBGV are intended for various scenarios, including peak exposures, e.g. air pollution, with mainly low exposure to the general public in inside environments and short peak sessions, e.g. when walking along busy roads. Indeed, the SCHEER report itself actually does rely on comparisons to HBGV, e.g. in its metal assessments (for example, P15,LN38). And yet it uses this flawed rationale to dismiss multiple published assessments from various sources including the US National Academies of Sciences, Engineering, and Medicine and Public Health England (P58,LN55-P59,LN4).

The 2nd hand exposure section P58,LN13-49, relies on a single study, referenced twice (1,2), where the approach to estimating exposure via exhaled breath is inaccurate. More accurate methods would be to use direct air concentration measurements or biomarkers of exposure in the bystanders, such as done in several publications that have been

referenced in discussions in the SCHEER report, but then not taken into account for the actual risk assessment. Not only is the method suboptimal to address bystander exposure, additionally, the exposure scenarios assumed are unrealistically high compared to the exposures assumed in the SCHEER report for the main user risk assessment. A more credible 2020 assessment from the UK Committee on Toxicity (3) concludes "E(N)NDS use is associated with some emissions into ambient air, including nicotine. For most health effects, the risks to bystanders will probably be low in conventional exposure scenarios, although pharmacological effects from exposure to nicotine in ambient air may occur in some individuals."

The conclusion on respiratory tract carcinogenicity due to nitrosamines and some VOCs exposure misleadingly states the human data is very limited and does not allow a conclusion (P61,LN35). However, that is because the SCHEER report does not include reference to any of the clinical biomarkers of exposure study data that exist, demonstrating exposures to nitrosamines and some VOCs from electronic cigarette use are low (4-9) and comparable to those from NRT (10).

The conclusion in 6.5.5.6 that the evidence base for cardiovascular effects for main users is strong, is inconsistent with the lack of long-term data identified in 6.5.4. And where longitudinal studies do exist, following cardiovascular health aspects of vaping, these indicate an improvement in cardiovascular health when switching from vaping (11-14), as reviewed in Buchanan et al. (15) The remaining lines of evidence relate only to nicotine exposure. Nicotine exposure to electronic cigarettes is broadly comparable to that from nicotine replacement product (e.g. 6-month biomarker data (10)), and thus, if the main CVD risk arises from the nicotine exposure, nicotine-related CVD risk from vaping would be expected to be comparable to that from NRT.

For conclusions on risk for the user, it should be considered that the vast majority of EU regular users are smokers or ex-smokers (16-19). Therefore, the relative risk versus smoking and resultant harm reduction should be an important consideration.

6.5.5 Risk Assessment- Part 2 References

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6.6 Role of E-Cigarettes in Initiation of Smoking

The Sheer Opinion concludes there is strong evidence that e-cigarettes are a gateway to smoking for young people.

Efforts to assess whether e-cigarette use causes cigarette smoking must consider "common liability," taking into account that predisposing factors of e-cigarette use are common to those of cigarette smoking. The common liability model, where inclination towards risk-taking and psychosocial processes can be factors, provides a parsimonious explanation of substance use co-occurrence (1-3).

SCHEER's Opinion proposed two hypotheses (gateway and renormalization), neither of which take into consideration the common liability model or providing evidence on causality among the studies synthesized. The systematic reviews in the Opinion do not support the gateway hypothesis. Glasser et al. (2019) notes that causal inferences are not supported by the evidence, and that youth using both e-cigarettes and cigarettes share a number of confounding factors that increase susceptibility to use either product (1). In particular, willingness to take risks, and perception of relative cigarette and e-cigarette risks and/or benefits all differentially influence cigarette smoking initiation (4). One cited study presents the inadequate control of confounding factors in the body of evidence and consequently challenges the existence of a gateway effect (5). The Opinion fails to account for various definitions of initiation of cigarette smoking among the studies. In most cases,

definitions of initiation are more consistent with experimentation (e.g., “ever use”) than true initiation (1, 6).

Independent organisations have criticised ‘gateway’ arguments and concluded that there is no reliable evidence of a gateway effect (7-9). Data from ASH UK finds that youth smoking rates are at an all-time low and youth use of e-cigarettes UK is rare and largely confined to those that already smoke cigarettes (10). Recent US National Youth Tobacco Survey data does not support a rise in youth nicotine dependence from e-cigarettes or a reversal in decreasing youth cigarette smoking prevalence (11).

The Opinion suggests that e-cigarette use plays a role in the initiation of smoking by emphasizing prevalence of e-cigarette awareness and use, preferences for flavours, levels of nicotine, and motivations for use. The Opinion fails to contextualize the findings and does not consider alternative hypotheses. An equally valid hypothesis is that the increase in e-cigarette use coupled with the recent and rapid decline of cigarette use among youth could mean that youth who are predisposed to smoke cigarettes are being redirected to a potentially less harmful product. A recent study showed that in the US, adolescents who (first) use e- cigarettes are less likely use cigarettes in future (12.) A 2020 study using survey data from the US Population Assessment of Tobacco and Health (PATH) Study showed that flavoured e-cigarettes were not associated with greater youth smoking initiation but with greater adult smoking cessation (13). Public health experts have recognised the important role that flavours have in increasing the potential for vapour products to act as a satisfactory alternative to cigarette smoking, and an important factor for smokers who are looking for alternatives to cigarettes (14-15). Flavours and efficient nicotine delivery play an important role in improving the overall appeal for less harmful nicotine products such as e-cigarettes, when compared to cigarettes (15-17).

The SCHEER Opinion fails to provide evidence that supports a direct association between e-cigarette use and resulting cigarette smoking or even define how the gateway theory can validly be tested and we respectfully request SCHEER to readdress their conclusion.

6.6 Role of Initiation- References

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analysis plan, and a plan for investigating heterogeneity. Additionally, the systematic review included a comprehensive search of MEDLINE, EMBASE, and PsycINFO using a reproducible search strategy. Unlike the Opinion, which arbitrarily excluded articles prior to 2015, our search dates were only restricted to exclude articles prior to 2007, because that was when e-cigarettes were introduced to the mass market in the US. For transparency, the full search strategy as well as the list of excluded articles are included in the report. The quality of included studies was assessed with the Downs and Black checklist, one of the most rigorous instruments for evaluating observational studies. Finally, the review assessed the strength of evidence using a standardized method, the Agency for Healthcare Research and Quality (AHRQ) Evidence Based Practice (EPC) grading system, integrating an assessment of the contextual questions examined in the review.

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6.7 Role of Electronic Cigarettes in Cessation

The SCHEER Opinion evaluated the strength of evidence as "weak" for cessation, and "weak to moderate" for reduction, lacking the proper justification for these determinations and ignoring the scientific evidence. While e-cigarettes are not authorised cessation devices, millions of smokers around the world have successfully switched to using e-cigarettes (1-6). Several studies, including randomised control trials and observational studies have shown that e-cigarettes are effective in helping adult smokers to quit smoking successfully (5,7-16). Rates of cessation using e-cigarettes have been reported as being as similar to or higher than standard cessation methods (3,17-18), even twice as effective as abstinence or NRT (19-20). A recent study of 13,057 subjects from 28 EU countries, found that compared with former smokers who had never used e-cigarettes; daily e-cigarette users were 5 time more likely to have quit smoking (21). In the EU, 6 out of 10 people reportedly took up e-cigarettes to stop or reduce tobacco consumption and was the highest mentioned reason for using e-cigarettes (61%) (22). More recently, a Cochrane review, across 50 global studies, including EU countries (Italy, Belgium, Greece an Poland) undertook an evidence synthesis that focused on the available RCTs and found

an association between e-cigarette use and higher quit rates vs NRT vs non-nicotine e-cigarettes vs support only/no support (23).

SCHEER treated cessation as a monolith, when in fact measures of cessation varied considerably and were often unique outcomes that should not be grouped as a collective, e.g., 7-day point prevalence abstinence is a far different outcome than 12-month abstinence. The outcome measures should have been described and appropriately considered as unique measures (24). Failure to do so compromises the validity of the weight of evidence evaluated.

Comparator groups and e-cigarette use definitions were highly variable in the included studies and included NRT, nicotine-free e-cigarettes, and support/counselling (19, 24-27). Frequency/regularity of e-cigarette use, which undermines any assessment of causality between regular e-cigarette use and cigarette smoking cessation (24) was not considered. Adjustment for confounders, between study groups within a given study were also not considered as well as a number of other important confounding factors. One study found African American participants were more likely to use e-cigarettes as a cessation aid compared to Caucasians ($p = 0.03$) (28).

Intention to quit and nicotine dependence varied across studies and study participants. Respondents with a higher motivation to quit are more likely to have a successful quit attempt.

In a recently completed systematic review and meta-analysis on associations between e-cigarette use among cigarette smokers and changes in continued cigarette smoking, 101 studies were identified as investigating the association between e-cigarette use and abstinence from cigarette smoking. Among those studies, the majority (76%) did not adjust for age, race, and sex (29).

Thus, pooling a body of evidence with high heterogeneity among studies, lacking adjustments for confounding factors that influence observed associations between e-cigarette use and smoking cessation outcomes, will inherently result in the evidence being graded as “weak.” This issue was discussed in a systematic review included in the Opinion’s assessment of cessation (26). We therefore respectfully request SCHEER to re-evaluate their conclusion, considering the available literature demonstrating their role in cessation and effectiveness in help smokers to quit.

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7. Minority Opinion

Remarkably, the SCHEER Preliminary Opinion does not include any minority opinions from the Committee. Other expert opinion and policy advisory document to date, prepared by expert bodies and regulatory agencies globally, have appropriately included extensively documented discussions acknowledging the public health principle of tobacco harm reduction and the consideration of e-cigarettes as a lower-risk alternative for smokers. The Opinion entirely neglects this important concept, and this 'elephant in the room' must be appropriately acknowledged and discussed. The Opinion's provision for Minority Opinions presents an opportunity to correct this important oversight by providing a truly balanced representation of a substantial volume of the published, peer-reviewed literature that addresses the role of c-cigarettes as a potentially powerful tool to achieve reductions in the risks to individual smokers and in the harms to the EU population from cigarette smoking.

A growing number of comparative studies have reported reductions in exposures to harmful chemicals, reductions in toxicity and biological effects in smokers who switch to e-cigarettes. Though BAT do not market e-cigarettes as smoking cessation devices, the well-respected Cochrane Collection recently published a comprehensive evidence-based report concluding moderate-certainty evidence that e-cigarettes with nicotine increase quit rates compared to e-cigarettes without nicotine and NRT; none of the included studies (up to 2-years duration) detected serious adverse events related to e-cigarette use.

The US National Academies of Science, Engineering and Medicine acknowledged the potential public health benefit of e-cigarettes in a published Report. The Report Committee comprised 13 academic scientific experts having extensive records of peer-reviewed publications on e-cigarettes. The Report was rigorously peer-reviewed before publication and was generated by inviting stakeholders to bring their collective evidence to the discussions.

The UK Royal College of Physicians (RCP) provided a detailed expert interpretive review and analysis of peer-reviewed, published literature documenting the harm-reduction potential of e-cigarettes for smokers who adopt their use as a replacement for cigarette smoking. In addition, an expert body convened by Public Health England (PHE) has produced and annually updated a series of major reports on vaping in England that offers expert analyses of the impact of e-cigarette usage on the public health, most recently in March 2020. These RCP and PHE reports reflect the opinions and comprehensive published literature analyses from biomedical and public health experts who have followed and considered the entire spectrum of new scientific findings that document the impacts of e-cigarettes on public health. Importantly, these major, comprehensive expert reports provide a balanced perspective on both the potential harms and the potential benefits of e-cigarettes. This objectivity is conspicuously absent from the Opinion, and SCHEER is well advised to follow the precedents by including a balanced consideration of the potential of e-cigarettes to provide public health benefits by accelerating the decline of smoking in the EU that may arguably outweigh any potential risks that e-cigarette use may pose.

The Opinion, as drafted, is deficient in its failure to acknowledge and fairly consider the abundantly documented risk-reduction potential and societal public health benefits of e-cigarettes, and the addition of a balanced discussion of what SCHEER apparently regards to be a minority opinion is a necessary addition to the Report. We respectfully request SCHEER consider and refer to the growing literature.

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8. References

The references section is one of the most important parts of an opinion or review article, as it clarifies the source of scientific fact and information. However, the Reference Section in the Opinion does not represent an unbiased cross-section of research – see statistics below. Specifically, only ~3% of references come from industry. Nearly half of the references are reviews covering many of the same (dated/older) primary studies, and the number of cited references with more current EU-marketed products are proportionally low (only 4% of references from 2020). Among the publications from academia, there is a bias towards studies originating from the US in general, but some of the individual EU academic labs are also over-represented (e.g. 14 references from Farsalinos lab). Finally, unpublished peer-review findings (a mix of unpublished studies, opinions, workshop reports and white paper - letters to the editor, etc.; e.g. McNamee p. 84) account for roughly 5% of the references. Although these non-peer-reviewed documents/publications add value and perspective, they should be used to support conclusions and not to derive them.

The Opinion's treatment and interpretations of systematic reviews are also inconsistent. Specifically, the Opinion reviewed several systematic reviews in Section 6.6, but there is no reference to a GRADE approach for the quality of evidence assessment. In Section 6.7, the Opinion specifies a GRADE rating for two systematic reviews; additionally, PRISMA guidelines and AMSTAR 2 would have rated the methodological and reporting quality of the reviews. This approach should have been applied throughout this evidence synthesis.

This section could benefit from additional attention to detail and format. Multiple errors and mistakes were noted, including inconsistencies in format style (e.g. 2 Etter et al. refs., P77), a number of duplications (e.g. Kim et al., P82), references published in more than one language at different times pointing to the same primary studies and drawing similar conclusions (e.g. Visser et al., P91), mislabeled/incorrect publication dates (e.g. Lee et al., P83,LN34 year is 2019), lack of full or correct citation details (e.g. Long, P84) and e-pub ahead of print citations used for publications dating back to 2016 (e.g. Malas et al., P84).

A large body of scientific evidence has not been considered by SCHEER, in particular the most recent scientific information. We respectfully request that SCHEER disclose the criteria used to select the scientific literature and also the methodology to evaluate the strength of the scientific information to inform this Opinion. We kindly refer SCHEER to the references provided to support the re-evaluation of their conclusions.

Author Affiliation – Institution/Organization:

Academia	61%

Industry	3%
Public Health/Govt	20%
Other/Mixed/Unknown	16%

Country of Origin:

U.S.	35%
Non-U.S.	65%

Type of Publication:

Standard/Guide/Position	14%
Review	28%
Unpublished/Non-peer reviewed	5%
Primary Research (not tabulated, but all remaining)	52%

Year of Publication:

Published 2014-2019 (stated target)	80%
Published 2020 (most current)	4%
Published before 2014 (possibly irrelevant or outdated)	16%

Annex 1

This Annex aims to provide the most appropriate methodology for the assessment of aerosol constituents in e-cigarettes. We respectfully request SCHEER to correct and amend the following:

(P95,LN5): refers to cigarette smoke, should this state e-cigarettes aerosol? As both e-liquid and aerosol condensate are liquid many methods consist simply of dilution with a suitable solvent and analysis using a combination of chromatographic separation and spectroscopic detection

(P95,LN14-17): no reference(s) provided.

(P95, LN18-20): “The agreement” to what? This text doesn’t refer to methods for PG detection/quantification. Reference 6 is mentioned, but not listed in Table A.1.1. Please can this be clarified?

(P95, L21-23) citations are inaccurate – only ref 10 included analysis of metals and these comprised only Ni, Pb and Cd, which were also detected in the Nicorette inhalator control. Ref 10 seems popular with the authors of the report – they re-cite it as ref 15 and ref 39. It is also cited in other sections as a source of emissions data but the data are not necessarily representative of current products – see final comment and table below.

(P95, L32-37): seems to classify carbonyls as nicotine degradation products, which is incorrect. As noted by the authors, vaping conditions affect carbonyl emissions significantly and, by their own admission (P35, L10) “Studies with controlled realistic (puffing) conditions are rare”, suggesting that the majority of carbonyls emissions data are not relevant for the assessment of consumer exposure.

(P95,L44) title of Table A.1.1 states “methods for nicotine and nicotine-related compounds”, however, the inclusion of a column for metals for example does not fit with the title.

(P97,L9) Table A.1.3, entry for “Heavy metals” under “Electronic cigarette liquid” lists Sn, Cu and Ni in the column providing instrument techniques

Considering the references from which the majority of emissions data are drawn (see list below), they were published between 2012 and 2014 and assessed only early generation e-cigarettes, typically disposables (15, 23) or early replacement liquids (17). These results may not be representative of the current generation of cartomizers and should be replaced or augmented by more current data:

Ref #15: Goniewicz et al 2014 (Approach: 10 cartridge + 2 cartomizer ecigs vs Nicorette; single port puff machine) - Devices were 150 puff equivalent cigalikes. Authors detected Ni, Pb, Cd, FA, AA in the Nicorette emission, suggesting a chemical background issue.

Ref #17: Kim et al 2013 (Approach: HPLC/MS/MS of 105 e-liquids from 11 manufacturers in Korea) - SPE and liquid partition. Total TSNAs 13±18ng/mL. NNN relatively high, proposed to be formed in e-liquid.

Ref #19: Lim & Shi 2013 (Approach: unable to find full manuscript online; cited by others) - Headspace GC/MS of aldehydes in liquids seems unlikely to measure carbonyl emissions accurately.

Ref #21: Schripp 2013 (Approach: abstract only) - 8m3 room is ‘close to real use’? Particle count and VOCs.

Ref #23: Williams et al 2013 (Approach: dissected 22 samples of a single cartomizer product) - Range of spectroscopic and imaging methods. Data are for early ecig. Later Williams papers also focus on disposable ecigs.

Ref #24: McAuley 2012 (Approach: Compared vapour of 4 ecig products to cigarette smoke in room air) - Vapour emissions (carbonyls, VOCs, PAHs, TSNAs) gave ‘no significant risk’ of cancer.

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

For references see Additional PDF attachment : 3. References- All Cited References

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PG/VG

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Nicotine, Alkaloids, TSNAs

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Annex 2

Since this Annex is intended to supplement Section 6.4, this needs to present the most up to date and relevant information regarding ingredients in use in EU e-liquids. The SCHEER review should focus on the ingredients and any associated risks, reported here, as opposed to scientific papers reporting on ingredients found in e-liquids from outside the EU or from before the introduction of the TPD in the EU. This is misleading and also does not represent the totallity of the current e-liquid offerings in the EU.

E.g., (P30,LN24-25) Ethylene glycol should be deleted as a solvent carrier in e-liquids because Annex 2 demonstrates it is irrelevant to current e-liquids within the EU (the original mention was presumably based on Hutzler et al 2014, which found it in pre-TPD German e-liquids).

Similarly, (P30,LN34; P30,LN37; P36,LN12-19; P55,L47) refer to reports of diacetyl being highly prevalent in e-liquids, referring to early US and pre-TPD reports, whereas this Annex shows no diacetyl in use in current EU e-liquids, so mentions of diacetyl-associated issues can be deleted throughout the SCHEER report.

Also, based on this information, all sections suggesting issues with TSNAs and tobacco alkaloids need to be reviewed in the report, whether this concerns risks to the main user or bystander risks. This list indicates tobacco extracts or oils are not used, so the only possible source of those compounds would be from impurities in the nicotine. Within the EU, TPD requires the ingredients used to be of high purity and various national standards (1,2) clarify that for nicotine, this means using pharmaceutical grade purity. So any concern around TSNAs and tobacco alkaloids from e-liquids is very low, and comparable to that from nicotine replacement products.

We therefore request that SCHEER ensure that information presented in the Annex and related chapters refer to the current status of e-liquid ingredients as per current regulations stipulated as part of TPD.

Annex 2 References

1. British Standards Institute. Vaping products, including electronic cigarettes, e-liquids, e-shisha and directly-related products. Manufacture, importation, testing and labelling. Guide. London: BSI; 2015. Ref. No. PAS 54115:2015.
2. Association Française de Normalisation. Electronic cigarettes and e-liquids – part 2: requirements and test methods for e-liquids. Paris: AFNOR; 2015. Ref. No. NF XP D90-300-2:2015.

Annex 4

SCHEER's selective evidence fails to meet the required standards of scientific advice set out in its Rule of Procedure, including the requirements of transparency and consideration of the best, and the most recent scientific and technical information available. The search strategy applied in the Opinion is not transparent and thus is not reproducible. Specifically, details on the databases used for the search, including Boolean search terms, were not provided. There is no list of excluded studies, nor are there details to identify a clear methodology for study inclusion or selection in the evidence synthesis.

The search strategy is not objective. The Opinion lacks a methodologically sound approach for study selection from the literature search results. Furthermore, without a justification for the identified search timeframe, the methodology could potentially lead to the unintended exclusion of important studies on specific topics that were published outside of a subjective timeframe. Finally, there is no method provided for the decision to include studies outside of the search timeframe. What is evident, the most recent and best available scientific studies were not selected to help inform an objective evaluation on the relative health risks of e-cigarettes compared to cigarettes.

The search strategy is not comprehensive. Presentation of Annex 4 and the overall number of studies indicates that a combined search was conducted for all outcomes investigated. Hence, search results may have been inadequate because search terms could interact with each other, excluding studies that may have been identified if an outcome-specific search had been conducted.

In conclusion, the Opinion should have followed a transparent, reproducible, comprehensive, and objective search strategy, as outlined in systematic review methodology guides (1,2).

Annex 4 References

1. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al., editors. Cochrane handbook for systematic reviews of interventions. 2nd ed. Chichester (UK): John Wiley & Sons; 2019.

2. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: Explanation and elaboration. PLoS Med. 2009;6(7):e1000100.

***Supporting Evidence for Section 6.5.4. Human Evidence of Health Impacts of Electronic Cigarettes (CVD)- Part 1**

Point #1:

This section on the potential for e-cigarettes to cause cardiovascular disease indicates throughout that more evidence is needed and more specifically, that long-term studies are required. However, in this report short-term and transient effect preclinical and clinical studies, along with hypothetical speculation, are being used to highlight long-term effects such as endothelial dysfunction, hypertension and cardiac arrhythmias. In addition, the manuscripts referenced highlight their own limitations, for instance Moheimani et al. (2017) could only rely on self-reporting of subjects who were asked not to smoke and indicated the unreliability of data collected on product use. As such, the data summarized in this report present an overstated perspective of the more fulsome information discussed.

These studies also hypothesise on the pathophysiological effects, which as mentioned are yet to be elucidated:"It has been hypothesized that via sympathetic nervous stimulation, as well as endothelial cell dysfunction and oxidative stress (Higashi et al., 2009, Moheimani et al., 2017), (atomized) nicotine impacts vasculature (Zhang et al., 2013) and arterial stiffness (Vlachopoulos et al., 2016) similarly to conventional tobacco smoking, ultimately inducing hypertension (Moheimani et al., 2017), well-established CVD risk factor". The report also suggests e-cigarette use leads to rapid surges in the number of circulating endothelial progenitor cells (EPCs) (Antoniewicz et al. 2016). This study carried out on 16 low level

smokers (<10 cigarettes per month) and failed to report on study limitations as per CONSORT guidelines. However, they do point out. "In humans, Kondo et al. demonstrated increased EPC levels following smoking cessation with and without nicotine replacement therapy, suggesting that nicotine per se did not alter EPC levels. Unfortunately, as we did not test nicotine free e-liquid in this study, it is difficult to determine if nicotine is responsible for the observed effects or not". This is in direct contradiction of the speculative discussion in this paper on how e-cigarettes may cause cardiovascular disease, based on a study on a very limited population, and all subjects were smokers. Generally, the studies referenced in this report only investigate acute effects of e-cigarette use in small populations and often the subjects are current/previous smokers. By not fully evaluating the impact of baseline health status and product use history, the results summarized in this report may

be confounded and not reflect the long-term health effects of e-cigarettes. Therefore, one must take into consideration that effects on cardio-vascular health could be a consequence of underlying disease.

Point #2: In addition, this section fails to put these potential effects of e-cigarettes in context with combustible cigarette use. There have been reports of significant improvement in endothelial function and vascular stiffness within one month of switching from smoking combustible cigarettes to e-cigarettes. Other studies report significant reduction in blood pressure with switching from smoking combustible cigarettes to e-cigarettes, as well as improvement in pulse wave velocity and reduction in malondialdehyde, an indicator of oxidative stress.

Point #3: Some of the references are old (e.g. Chen 2013), and cross-sectional studies. This asks the question how relevant this information is, with regards to products and e-liquid formulations currently on the market, and makes it difficult to distinguish cause and effect.

Point #4: Some statements are not referenced (e.g. Recent findings demonstrate that volatile
liquids containing nicotine may induce adverse cardiovascular effects attributed to its toxic impact on myocardial cells p.48), incorrect references are used (p. 48, Farsalinos et al. 20141) and some references do not support the claims being made (p. 48, Franzen et al. 20181).

Point #5: CVD pathogenesis is multifactorial, therefore, the notion that the use of cigarettes or e-cigarettes are sole contributors is misleading. This report fails to delineate the long-term effects of e-cigarette use from combustible cigarette use on development of CVD. Vascular pathology affects cardiac, cerebral and other end organ perfusion and lead to acute, chronic disease state and ultimately catastrophic event. In order to delineate the effect of e-cigarette use from combustible cigarette use, long-term studies (3-6 month) with clearly defined baseline health/ vascular status assessment to assess physiological response to exclusive e-cigarette use will be more relevant in discussions around specific contribution of e-cigarettes in CVD.
We believe that in use of combustible cigarettes, combustion of plant materials and inhalation of by products of combustion are the main contributor in development of pulmonary and vascular pathology including acute/sub-acute inflammatory status prior to pathogenesis. The current literature cited by this report does not adequately address baseline health status of subjects such as, relevant baseline assessment of indices of pulmonary/ vascular health status (such as vascular tone, flow rate via ultrasound, laboratory indices of known inflammatory markers at baseline), social history (Life style history/habits), and vascular pathology risk stratification based on number of years (pack years) subject had used combustible cigarette products to delineate the long term effects (3 to 6 month outcome results) of e-cigarette use compared to combustible cigarette. In addition, when considering the impact of nicotine on CVD, it is important to consider other sources of data available for nicotine-containing tobacco products on CVD. There is a

significant body of epidemiological data available for moist tobacco and snus use, collectively smokeless tobacco (ST), which is another product category that expose users to nicotine in addition to other potential toxicants. Six cohort studies, two conducted in U.S. populations (Accortt et al. 2002; Henley et al. 2005) and four conducted in Swedish populations (Bolinder et al. 1994; Johansson et al. 2005; Haglund et al. 2007; Hansson et al. 2009) that examined the association between ST use and ischemic heart disease (IHD) mortality or incidence. In some studies, the term coronary heart disease (CHD) is used instead of IHD; despite the difference in nomenclature, these two terms refer to the same outcome. For the purposes of this discussion, the term "IHD" is used, except where the authors specifically investigate CHD. Across all studies, IHD was defined using the International Classification of Diseases, Eighth Revision (ICD-8) codes 410-414, ICD-9 codes 410-414, or ICD-10 codes I20-25. The literature identified provides no consistent demonstration of an association between ST use and IHD mortality or incidence. Of the six studies identified, only two studies (Bolinder et al. 1994; Henley et al. 2005) provide any indication of a positive association between ST use and IHD. Both of the studies reporting positive associations assessed tobacco use many years prior, and it is likely that the constituents of the ST products used at that time included substantially higher toxicant levels compared to those found in modern products. Accortt et al. 2002 identified no association within their study, and ST users would have used these older products as well. Findings from all six studies
were limited by their tobacco usage assessments, as tobacco usage was assessed either at baseline or once during follow up, and nothing is known about changes in habits that may have occurred during each study's respective follow-up period. Results from the study with the shortest follow-up and whose methods were least likely to be substantially impacted by misclassification20 (Hansson et al. 2009) indicate no association between snus use and IHD hospitalization and deaths. In general, this report is not a balanced review of the literature especially as e-cigarette studies with positive CVD outcomes are not discussed. In fact, for the Benowitz and Burbank 2016 reference, only a table of potential diseases associated with nicotine use is included. Yet, this paper should be central to this section as it attempts to show from the current literature where e-cigarettes are in terms of potential cardiovascular disease risk in comparison to smoking combustible cigarettes. It also states: "While people with established CVD might incur some increased risk from e-cigarette use, the risk is
certainly much less than that of smoking. If e-cigarettes can be substituted completely for conventional cigarettes, the harms from smoking would be substantially reduced and there would likely be a substantial net benefit for cardiovascular health". This agrees with other publications which indicate that although e-cigarettes are not harmless, in terms of the risk continuum they are likely to be less harmful than combustible cigarettes. Overall, the evidence suggests that chemicals other than nicotine are responsible for the elevated risks of myocardial infarction and stroke in smokers. For example, in patients with cardiovascular disease, the risks of using nicotine products such as nicotine replacement therapies (NRT), if any, are much lower than those of smoking, and the benefits of NRT far outweigh the risks of continued smoking in such patients. In SCENIHR's evaluation of ST, they did not make the same strong association between nicotine and CVD as this report. SCENIHR noted transient HR and BP increases immediately following use (as did SCHEER),

but only speculated that it may cause in endothelial dysfunction—which is not strong evidence (i.e., weight of association) for a link between nicotine and CVD.

Finally, SCHEER panel's conclusions regarding nicotine are at odds with the US FDA's public statements about the role of nicotine in disease: "This mix of chemicals—not nicotine—is what causes serious disease and death in tobacco users." This is supported by the UK Royal College of Physicians who have made public statements about the role of nicotine in disease development in contrast to this report.

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Supporting Evidence for Section 6.5.4. Human Evidence of Health Impacts of Electronic Cigarettes (CVD)- Part 1 References

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