



**E-cigarette
Research**

Dr. Farsalinos' Scientific Blog

“ THE CASE FOR FLAVOURS IN TOBACCO HARM REDUCTION, TO SAVE LIVES

A multi-dimensional review of
the use of flavours in tobacco
harm reduction
& nicotine vaping
products

(Otherwise called
e-cigarettes or ENDS)

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(FLAVOURS)





CONTENTS

1. SUMMARY	3
2. INTRODUCTION	4
a. Why flavours are important – World Health Organization (WHO) and tobacco control	
b. What is tobacco harm reduction (THR)?	
c. Role of ENDS / nicotine vaping products in THR	
3. FLAVOURS USED IN TOBACCO HARM REDUCTION (THR)	12
a. Flavours in ENDS /nicotine vaping products - the basics	
b. Current use of flavours in ENDS / nicotine vaping products	
4. SMOKING CESSATION AND FLAVOURS	16
a. Key link between (mostly flavoured) ENDS / nicotine vaping products and smoking cessation	
b. Medicinal Nicotine Replacement Therapy (NRT) and its use of Flavours for Smoking Cessation (as included in the WHO List of Essential Medicines)	
5. SCIENCE DIMENSION OF FLAVOURS USED IN ENDS / NICOTINE VAPING PRODUCTS	21
a. ENDS / Nicotine Vaping Products Chemistry	
b. Safety studies of flavoured E-liquid (used in ENDS)	
c. Social & Behavioural Sciences: Surveys and Usage Patterns	
6. PUBLIC HEALTH DIMENSION: WHAT PUBLIC HEALTH EXPERTS SAY ABOUT FLAVOURS IN NICOTINE VAPING PRODUCTS	33
a. Netherlands Government consultation – February 2021	
b. Health Canada Consultation – September 2021	
7. CONSUMER DIMENSION: WHAT THE CONSUMERS SAY ABOUT FLAVOURS	42
a. Netherlands Government consultation – February 2021	
b. European Union (EU) SCHEER Report - 2021	
c. Health Canada Consultation – September 2021	
8. UNINTENDED CONSEQUENCES OF FLAVOUR BANS.....	46
a. Potential unintended consequences of flavour bans (in ENDS / nicotine vaping products)	
b. Impact of flavour bans on usage and smoking cessation	
9. CONCERNS THAT NEED TO BE ADDRESSED	50
a. ENDS / Electronic cigarette use by never smokers and youth	
b. Safety aspects of flavours in ENDS / nicotine vaping products	
10. REGULATORY CONSIDERATIONS	56
11. CONCLUSIONS	60
12. RECOMMENDATIONS.....	62
ABOUT THE AUTHOR	65
BIBLIOGRAPHY	66

1. SUMMARY

Smoking is one of the most lethal addictions, with more than 8 million premature deaths being recorded annually from smoking-related diseases, according to the WHO⁽¹⁾. While nicotine is the main substance linked to dependence, harm is predominantly caused by combustion products or other harmful compounds present in cured tobacco⁽²⁾. Due to the difficulty in quitting smoking and the relatively low effectiveness of smoking cessation medications⁽³⁾, the concept of tobacco harm reduction, a strategy of providing nicotine through less harmful products, has generated a lot of interest. Electronic cigarettes are nicotine products that do not contain tobacco and are nowadays widely available globally⁽⁴⁾. This review evaluates the use of flavours in tobacco harm reduction products, specifically, nicotine vaping products. It highlights the link between (flavoured) vaping products and smoking cessation^(3,5-9), and the potential benefits and risks for public health of flavours availability.

Right now, we are at a turning point, with many governments in the process of examining, or re-examining the role of reduced risk nicotine-based products, and the use of flavours in these categories. This represents an opportunity to develop tobacco control strategies which embrace the concept of harm reduction to facilitate the move of smokers away from cigarettes toward less harmful nicotine delivery products, while preventing the adoption of regular nicotine-containing or tobacco product use among underaged persons (younger than 18 years). Well-regulated use of flavours can and should be considered as a valuable tool to help prevent disease and save the lives of adult smokers who cannot or will not quit by themselves or with other approved methods.

As an ex-smoker and current vaper, who has done extensive research on the subject of e-cigarettes (see my website ecigarette-research.org⁽¹⁰⁾), I strongly encourage all stakeholders to engage in the debate on the risks and benefits of tobacco harm reduction, specifically vaping products. As the focus of opposition to THR seem to be on preventing youth initiation of smoking and vaping (rightly so), this review is to contribute towards a “whole of society” solution to combustible tobacco-related disease and premature death.

2. INTRODUCTION

This multidimensional review examines the science, consumer insights, risks and regulatory considerations pertaining to flavours used in tobacco harm reduction, specifically in nicotine vaping products (otherwise called e-cigarettes or “electronic nicotine delivery systems” or ENDS). These terms are used interchangeably in this review, although it all refers to the same category of devices.

This form of harm reduction is one of the most exciting opportunities to help prevent tobacco-related disease and premature death, by persuading cigarette smokers who can't quit, to switch to less harmful alternatives. The main advantage of e-cigarettes is that they resemble the act and experience of smoking. While this has been presented as a drawback that could renormalize smoking, it is in fact important for smokers to substitute the experience and pleasure they perceive from smoking with a similar experience from other products.

Currently, almost all of the vaping products make use of flavours, to encourage adult smokers to consume nicotine using a liquid heated by a vaporizer, paired with various flavours to offer a better taste to users. Products without added flavours are almost flavourless since the main ingredients, glycerol and propylene glycol, only have a faintly sweet taste.

The key point is that it facilitates smoking cessation, therefore preventing disease and saving lives.

Prof. David Levy, veteran tobacco control researcher from the USA, calculated that if all adult smokers in the USA were to switch to nicotine vaping products, from 2013 to 2060, a staggering 1,8 million deaths would be avoided, and 38,9 million life years saved⁽¹¹⁾.

Unfortunately, several governments are contemplating banning flavours in ENDS, apparently to prevent youth initiation. This review argues for the responsible and regulated use of flavours, to maximise the harm reduction effect of ENDS and its role in smoking cessation.

If bans were allowed, it would ultimately drive consumers to tampering, illicitly traded products, towards the black market, or back to traditional cigarettes⁽⁶⁾.

Given that forecast, legislators should carefully weigh the risks and benefits of flavoured nicotine vaping products⁽¹²⁾, before considering the implementation of vaping flavour bans.

During 2021, few peer-reviewed articles carry more weight than the publication by 15 former Presidents of the Society for Research on Nicotine and Tobacco Products (SRNT), who said: “Because evidence indicates that e-cigarette use can increase the

odds of quitting smoking, many scientists, including this essay's authors, encourage the health community, media, and policymakers to more carefully weigh vaping's potential to reduce adult smoking-attributable mortality"⁽¹²⁾.

This was echoed by a letter⁽¹³⁾, signed by 100 world-class, independent scientists, including myself, directed to the World Health Organization (WHO) and its member states, on the eve of the Conference of Parties (COP) 9 in Geneva from 8-13 November 2021. The central call was for member states to consider:

“Over the last decade, innovation in the tobacco and nicotine marketplace has meant there are now many nicotine products available that do not involve combustion of tobacco leaf and inhalation of smoke. These smoke-free products include vaping products, novel oral nicotine pouches, heated tobacco products, and low-nitrosamine smokeless tobacco, such as snus. Cigarettes and other smoked tobacco products are responsible for the vast majority of the deaths caused by tobacco use globally. Smoke-free nicotine products offer a promising route to reducing the harms arising from smoking. There is compelling evidence that smoke-free products are much less harmful than cigarettes and that they can displace smoking for individuals and at the population level”⁽¹³⁾.

a. Why flavours are important: World Health Organization (WHO) and Tobacco Control

The WHO constitution states that its objective shall be the “*enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition*”⁽¹⁴⁾.

In the same spirit, Article 1 of the Framework Convention on Tobacco Control (FCTC)⁽¹⁵⁾ – the ground-breaking international agreement that was signed in 2003 – states that “*tobacco control itself means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke*”.

Since the 1960s, when the first reports from the Royal College of Physicians in the UK⁽¹⁶⁾ and the Surgeon General in the United States were released⁽¹⁷⁾, it has been well established that smoking is a major preventable risk factor for a variety of diseases, and an addictive habit responsible for substantial morbidity and mortality. The World Health Organization reports that 22.7% of the global population above the age of 15 were smokers in 2015, which translates to approximately 1.1 billion people⁽¹⁸⁾. Even more worryingly, 1 billion people are expected to die prematurely from smoking-related disease during the 21st century. In the United States, it has been estimated that approximately 480,000 people die annually from smoking-related diseases, while the respective death toll in Europe is estimated at 700,000^(19, 20).

This substantial health, economic and social burden of smoking has resulted in intense efforts to regulate tobacco cigarettes, with the main purpose being to minimize addictiveness, appeal and use by the population. A landmark, global, coordinated effort was the Framework Convention on Tobacco Control (FCTC), established in 2005 and comprised of 168 signatory countries. The goal and responsibility of the FCTC was to provide proper guidance and a strategic plan for policies that could be implemented globally. In that context, the MPOWER was created in 2008, with the core principles being to develop policies to prevent smoking initiation and promote smoking cessation, educate people about the risks of smoking, ban marketing and advertisement of tobacco products and raise taxes as a measure to discourage use⁽²¹⁾. While these efforts were key in reducing prevalence, smoking remains a prevailing public health issue.

b. What is Tobacco Harm Reduction (THR)?

Harm reduction initially referred to policies, programs and practices that aim to attenuate negative health, social and legal impacts related drug use, drug policies and drug laws⁽²²⁾. Harm reduction is fundamentally based on justice and human rights, focusing on positive change and on working with people without judgement, coercion, discrimination, or requiring that they stop using drugs as a precondition of support. Some characteristic interventions are the needle and syringe exchange programs, and opioid substitution therapy for intravenous drug users. Such measures have been actively endorsed by authorities such as the World Health Organization and the Red Cross, as well as several countries through national legislation^(23,24). These measures are known to reduce the risk of blood-borne infectious diseases such as hepatitis and HIV, are cost effective and result in improved quality of life⁽²⁵⁻²⁷⁾. However, the harm reduction concept has a much wider perspective and is applicable even in common daily activities. The use of helmets and seatbelts is a typical case of a harm reduction approach since it does not eliminate the risk for injury or death in an accident, but it reduces the risk. Even medicine could be considered as a harm reduction science since, except for some infections, most diseases are only treated but not cured. This means that therapeutic measures are applied in order to reduce symptoms, reduce the consequences, reduce the decline in quality of life and reduce the inability caused by diseases.

Similar to the generalized concept of harm reduction, tobacco harm reduction refers to the reduction of harm associated with the use of combustible tobacco products. It was initially conceived by the British scientist Prof. Michael A.H. Russell, who mentioned in 1976 that “smokers smoke for nicotine but die from tar”⁽²⁸⁾. This statement is closely linked to the distinction between the dependence potential of smoking, in which nicotine plays an important role, and the harm caused by smoking, which is mainly caused by combustion products and other toxins present in cured tobacco leaves.



The need for tobacco harm reduction is linked to the difficulty in quitting smoking and the limited effectiveness and appeal of smoking cessation interventions. Medications used to quit smoking are available for many years, relatively safe and effective compared to placebo⁽²⁹⁻³³⁾. However, their long-term success rate is limited. A systematic review and meta-analysis of the effectiveness of nicotine replacement therapies found that < 7% of smokers remained abstinent at 1 year⁽³⁴⁾. Cohort studies of real-world use of these medications available over the counter, raise further doubts about their effectiveness compared to quit attempt without the use of any aid⁽³⁵⁾. Pharmaceutical nicotine products characteristically deliver nicotine much slower compared to tobacco cigarettes. At the same time, they do not address the psycho-behavioural aspect of smoking dependence⁽³⁶⁻³⁹⁾. Although better than pharmaceutical nicotine, oral smoking cessation medications still have a relatively low success rate⁽⁴⁰⁾. In real-world clinical use, their effectiveness may be even lower⁽⁴¹⁾. Added to the above, a substantial proportion of smokers are not willing to use medications or professional assistance for smoking cessation. As a result, quitting without any aid remains the most popular, but also the most ineffective smoking cessation method^(42,43). Therefore, most smokers are unwilling or unable to quit smoking with currently approved methods, while others want to continue experiencing the “positive” effects of smoking (in terms of the behavioural experience and nicotine intake) and are unlikely to use medications that do not provide the “pleasure” perceived from smoking⁽⁴⁴⁾.

One of the first suggestions to apply a tobacco harm reduction strategy was through the use of smokeless tobacco products^(45,46). A characteristic example of a country where such products are popular, particularly among men, is Sweden. While tobacco use among Swedish men has not been eliminated, the vast majority of men use snus instead of smoking tobacco cigarettes. Still, the death rates from cardiovascular disease, lung cancer and any type of cancer in Swedish men is the lowest in the European Union⁽⁴⁶⁾. However, and despite the overall acceptability of the harm reduction principles for daily activities and for intravenous drug users, tobacco harm reduction remains a controversy within the public health community⁽⁴⁷⁻⁵⁰⁾.

Despite the global controversy over the value of tobacco harm reduction and e-cigarettes, some organizations have stood out to support the prospects of using these nicotine products as part of the solution to the smoking problem. In landmark reports in 2014 and 2016, Public Health England and the Royal College of Physicians (RCP)⁽²⁾ estimated that the hazard to health arising from e-cigarettes available today is unlikely to exceed **5% of the harm from smoking tobacco**.

In other words, tobacco and nicotine products can be stretched out along a harm continuum⁽⁵¹⁾, with cigarettes at one end and oral nicotine pouches that do not contain tobacco on the other. In between sit lower-risk smoke-free products such as heated tobacco products, e-cigarettes and smokeless tobacco pouches (e.g., Snus).

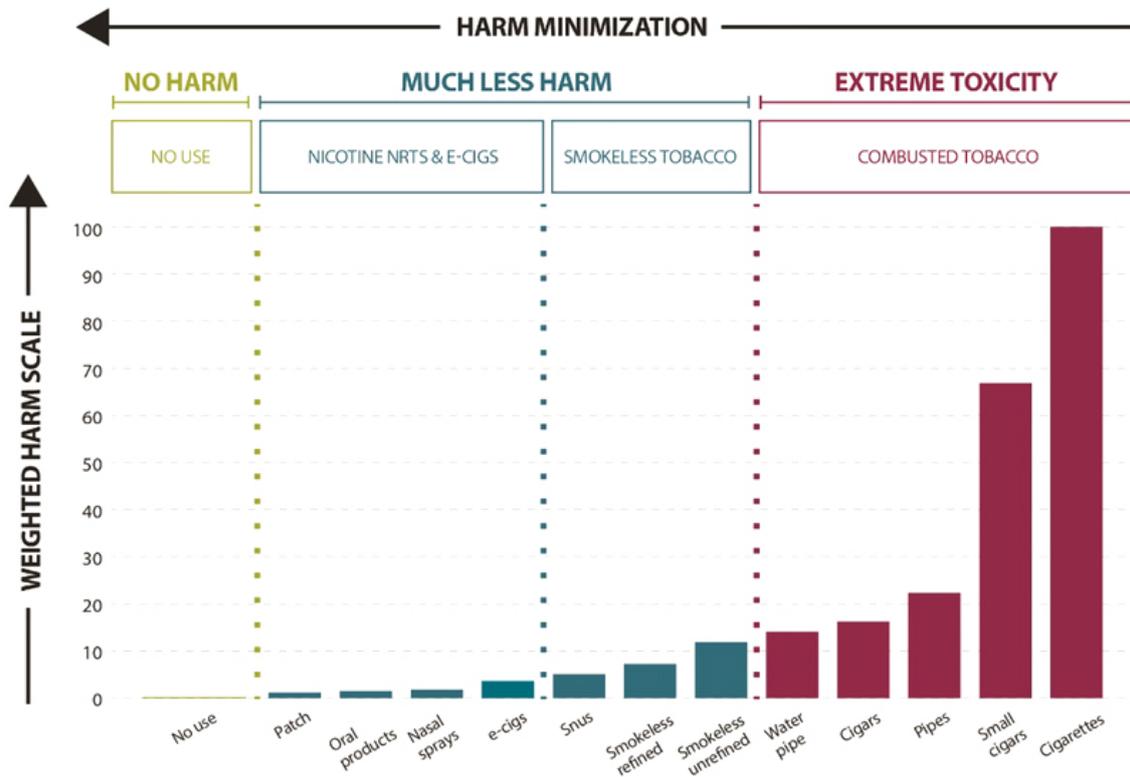


Table 1: Illustration of harm minimization continuum by David Abrams et al ⁽⁵¹⁾

Unfortunately, there seems to be a conflict between those who want to promote tobacco harm reduction (THR) efforts, as part of tobacco control, and those who want to eliminate tobacco and nicotine altogether – but this is unnecessary. Because THR has at its heart the very same guiding principles as those who want to eliminate tobacco altogether: to prevent or reduce tobacco-related health risks, diseases and premature deaths. In short, to save lives.

Given the expected net health benefits of switching from cigarettes to any of these other products, this trend should be welcomed and accelerated. It is as simple as that. And consumers – indeed, the public in general – must be educated about the relative harms of products that contain nicotine, and their benefits, too.

c. Role of ENDS / nicotine vaping products in tobacco harm reduction (THR)

Electronic cigarettes, **otherwise known as nicotine vaping products or electronic nicotine delivery systems (ENDS)** are devices consisting of the battery part (usually rechargeable lithium battery), and a liquid container called “atomizer”, where the liquid is stored and aerosolized by heat generated from electrical current applied to a resistance. The resistance is a metal wire wrapped around a wick, usually composed of cotton. The main ingredients of the liquid are glycerol, propylene glycol, flavour-

ings and nicotine, although nicotine-free liquids are also available. Different types of devices are available, from first generation, cigarette-like devices that resemble tobacco cigarettes in size and shape, to complex devices consisting of higher-capacity lithium batteries, electronics to adjust power settings and atomizers that can be refilled with liquid and have adjustable airflow⁽⁵²⁾. Despite containing nicotine, which is extracted from tobacco leaves, electronic cigarettes are in reality non-tobacco products because they do not contain cured tobacco.

Electronic cigarettes have been growing in popularity, especially during the last decade. While invented in 2004, awareness and use has grown, especially during the past 10-12 years⁽⁵³⁻⁵⁸⁾. In the United States alone, the sales value increased from \$20m in 2009 to over \$1 billion in 2013⁽⁵⁹⁾. In Europe, approximately 48.5 million residents reported being ever electronic cigarette users in 2014, with 7.5 million reporting current use⁽⁴²⁾. In the United States, approximately 10.9 million adults were current electronic cigarette users in 2019 compared to 40.8 million who were using any combustible tobacco product⁽⁶⁰⁾.

The exponential increase in awareness and use of electronic cigarettes has generated substantial concerns about their public health impact. Some consider that electronic cigarettes could supplement other tobacco control measures by helping more smokers to quit, thus accelerating the smoking decline. This would result in a net public health benefit⁽⁶¹⁻⁶³⁾. Others consider electronic cigarettes could jeopardize the progress made over the past decades by renormalizing the act of smoking, making them socially acceptable⁽⁶⁴⁻⁶⁶⁾.

Understanding the public health impact of electronic cigarettes is a complex and difficult task. These products can have beneficial and adverse public health effects, depending on several factors which include the products characteristics as well as their appeal and use patterns by population subgroups.

The safety/risk profile of electronic cigarettes is crucial in the assessment of their public health impact. Tobacco cigarettes emit several toxic and carcinogenic compounds, many of which are combustion products. Smoking is a risk factor for several diseases, mainly of the cardiovascular and the respiratory system, as well as cancers of the lungs and other organs. Compared to non-smokers, smokers have a higher risk for cardiovascular death. In people aged 50 years or less, smokers have a 4-fold higher risk of developing myocardial infarction compared to non-smokers of similar age⁽⁶⁷⁾. The myocardial infarction risk seems to be associated with both smoking duration and cigarette consumption⁽⁶⁸⁾. The risk for developing chronic obstructive pulmonary disease is also increased by 3 to 5-fold⁽⁶⁹⁾. Smoking is also the leading cause of lung cancer deaths^(70,71). Importantly, smoking cessation can be beneficial in lowering the risk for future development of disease or halting disease progression⁽⁷²⁻⁷⁴⁾. However, it may take several years until the disease risk for former smokers approximates the risk of never smokers⁽⁷⁵⁻⁷⁸⁾. Therefore, the assessment of the relative risk of electronic



cigarettes compared to tobacco cigarettes is important if electronic cigarettes would be used as smoking substitutes as part of a tobacco harm reduction strategy. This may be important even for secondary prevention, since smoking cessation improves prognosis. However, there are many smokers who fail to quit even after they develop smoking related disease^(79,80). Additionally, the absolute safety/risk profile of electronic cigarettes is important in order to determine both the residual risk for smokers who quit by using electronic cigarettes, compared to those who without the use of any substitute, and the risk for those who initiate electronic cigarette use while they had never smoked.

A second factor that needs to be examined is the effect of electronic cigarettes on smoking habits and cigarette consumption. Electronic cigarettes could have a role as smoking substitutes for those unable or unwilling to quit by themselves or with the use of smoking cessation medications and psychological support. Therefore, their public health impact is directly related to their effectiveness in promoting smoking cessation. A potential benefit may be expected from reduced smoking consumption could also result in some benefit, although this is expected to be lower compared to complete abstinence. Many studies suggest that there is dose-response relationship between disease risk, as well as all-cause mortality and smoking duration and consumption^(68,81,82). However, it is still unclear how reduction in cigarette consumption affects disease risk⁽⁸³⁻⁸⁶⁾. There is an inconsistent correlation between reduced consumption and reduced toxin exposure, which creates difficulties in quantifying the level of risk reduction. Therefore, complete abstinence from the use of any combustible tobacco product should be the goal of all electronic cigarette users.

An additional factor that needs to be examined is the appeal, popularity, prevalence and patterns of electronic cigarette use according to the smoking status. Electronic cigarettes use involves inhalation of an aerosol that may contain nicotine, using rituals that closely resemble the act of smoking. Thus, there is a dependence potential, particularly if sustained long-term use is adopted by people who had never smoked in the past. This would result in added health risk. Therefore, particular attention should be paid to the past smoking status of electronic cigarette users, referring to the period before electronic cigarette use initiation. An additional concern is the adoption of use by adolescents. It is well-known smoking initiation during adolescence is a predictor of regular and sustained smoking⁽⁸⁷⁻⁹²⁾. Adolescents appear to be more prone to test things and engage in risky behaviours. Thus, electronic cigarettes could attract them due to a tendency to experiment out of curiosity. However, they could also “distract” from use of tobacco cigarettes. Both aspects should be examined. Another possibility is that electronic cigarettes might act as a gateway to smoking, i.e., promote subsequent smoking initiation. This means that people who have never and who would have never smoked had electronic cigarettes not been available, become addicted through sustained electronic cigarette use and subsequently become smokers. Finally, it is equally important to examine the ac-

ceptability and appeal of electronic cigarettes in the smoking population. Smoking cessation aids need to be safe, but they must also be appealing and satisfactory for smokers. A characteristic example showing the importance of product popularity comes from the use of snus by Swedish men. Ramström et al analysed aggregate data from 2003 to 2011 and found that 30.8% of Swedish men used tobacco daily, with 20.2% using snus and 12.3% using tobacco cigarettes⁽⁹³⁾. Most of snus users were non-smokers, and snus use was reported to be the most popular smoking cessation aid. The unique characteristic of snus being the predominant tobacco product used by Swedish men is probably responsible for the low death rates from cancer and cardiovascular disease in the country⁽⁴⁶⁾.

All the above represent the main challenges and research areas that need to be examined in order to determine the public health impact of electronic cigarettes. An overview of these challenges is presented in **Table 2**. A simplified formula was suggested as a measure of the public health impact of electronic cigarettes⁽⁹⁴⁾:

$$\text{Public health impact}_{EC} = (\text{hazard}_{SM-EC} \times \text{smoking cessation}) - (\text{hazard}_{EC} \times \text{use among non-smokers}) - (\text{hazard}_{SM} \times \text{smoking initiation})$$

where EC: electronic cigarette; SM: smoking; SM-EC: difference in hazard between smoking and electronic cigarette use; hazard_{SM}: refers to smoking initiation due to electronic cigarettes (gateway to smoking effect).

The formula suggests that acceptability and appeal to smokers, leading to smoking cessation or reduction, and to non-smokers are major determinants of the overall population health effects of these products.

Table 2: Determinants of the public health impact of electronic cigarettes

Factor	Details
Product hazard	The safety/risk profile of electronic cigarettes, both relative to smoking and in absolute terms, needs to be determined. This will inform smokers about the relative risk and the residual risk if they quit by switching to electronic cigarettes and will define the risk for never smokers who initiate electronic cigarette use.
Effectiveness in smoking cessation and reduction	Studies need to assess their real-world effectiveness in promoting smoking cessation, but also any possible unintended consequences such as delaying or hindering smoking cessation.
Appeal and popularity in different population subgroups	Ideally, electronic cigarettes should be used only by current and former smokers, as smoking substitutes. Their popularity among never smoking adults needs to be monitored. Additionally, monitoring use by adolescents is important to determine whether it acts as a gateway to smoking or as a “distraction” from smoking, thus preventing smoking initiation.

3. FLAVOURS USED IN THR

a. Flavours in ENDS / Nicotine Vaping Products – the Basics

Flavourings are important for electronic cigarette liquids because they have no flavour without the use of additives. Only 1% of users were consuming flavourless liquids in an online survey⁽⁹⁵⁾. In another survey, users were consuming multiple types of flavours on a regular basis, switching between flavours daily or even within the day⁽⁹⁶⁾. Tobacco flavours appear to be more popular at electronic cigarette use initiation, as expected. However, there was a transition to different flavours over time, with fruit eventually becoming the most frequent flavour. Flavours were reported to play an important role in the effort of smokers to reduce or quit smoking. Smoking cessation was independently associated with the number of different flavours used regularly. More recent studies have shown that a substantial proportion of smokers initiate electronic cigarette use consuming non-tobacco flavours and subsequently quit smoking^(97,98).

There are three main types of flavourings used in food products. Natural flavourings are obtained from plant or animal raw materials. Nature-identical flavouring substances are synthetically produced natural compounds. Artificial flavourings are compounds that do not exist in nature. The Flavour and Extract Manufacturers Association of the United States (FEMA) launched a program examining the safety of flavouring substances in 1959⁽⁹⁹⁾. The FEMA GRAS program has become the longest-running and most widely recognized initiative of its kind, with specific criteria being set for the establishment of GRAS status for each compound^(100,101).

In the United States, the Food and Drug Administration (FDA) is the primary regulatory agency for food products and additives⁽¹⁰²⁾. In Europe, the European Food Safety Authority (EFSA) is responsible for such regulations. In 1996, Regulation (EC) No 2232/96 Established the procedure for the assessment of the safety of flavouring substances⁽¹⁰³⁾, while additional guidance was released by EFSA in 2010⁽¹⁰⁴⁾.

More than 7000 different flavours are available on the electronic cigarette market⁽¹⁰⁵⁾. Despite being approved for food use; this refers to ingestion only. FEMA clarified this in a statement in 2013, which was updated in 2016⁽¹⁰⁶⁾. Inhalation through electronic cigarette use results in exposure of the lungs to the aerosolized flavouring chemicals. Additionally, the aerosol is rapidly absorbed and bypasses the liver. There are concerns that some flavouring substances may adversely affect the respiratory health of people working in manufacturing facilities⁽¹⁰⁷⁾. This refers to occupational exposure, which usually involves continuous 8-hour daily, while electronic cigarette use is intermittent in nature. It is debatable if occupational exposure limits can be applied to consumer exposure⁽¹⁰⁶⁾. At the same time, however, it should be empha-

sized that smokers are exposed to the toxins of cigarette smoke; thus, it may be a reasonable approach to use guidance from occupational exposure guidelines in the risk assessment of electronic cigarettes if the latter are used as a harm reduction product, especially when no other data are available⁽¹⁰⁸⁾.

Many years of research are needed in order to study the effects of all the flavouring compounds when inhaled, with particular interest on the effects of exposure on the upper and lower respiratory tract. At the same time, flavourings are essential in the acceptability and appeal of electronic cigarettes when used as substitutes for smoking⁽⁹⁶⁾. Thus, restrictions on the use of flavours would reduce the acceptability of electronic cigarettes to smokers. In 2014, the EU introduced legislation for electronic cigarettes which did not implement any restrictions on flavours but allowed member states to adopt different rules⁽¹⁰⁹⁾. Importantly, only ingredients of high purity should be used, and there was flexibility to withdraw from the market products could pose health risks.

b. Current use of Flavours in ENDS / Modern nicotine vaping products

After a basic review of more than 600 articles pertaining to flavours used in THR, here are some observations, which will be elaborated in more detail in future publications:

(i) Numbers of flavoured e-liquids:

Each major market appears to have more than 10,000 flavoured e-liquids on sale. Surveys show that in 2017 there were 15,586 distinct flavoured e-liquids sold in the US (source: internet survey), 32,407 different e-liquids in the UK (source: regulatory submissions), and 19,266 different e-liquids sold in the Netherlands (source: regulatory submissions).

These numbers may be influenced/perturbed to some degree by several factors, including the introduction of the EU TPD in 2016, and more recently by FDA premarket authorisation procedures. The numbers above also include instances of the same flavour with different nicotine strengths. Also, the UK and Netherlands values are for all e-liquids, including unflavoured liquids (a relatively minor category). However, despite these factors, the number of flavoured e-liquids sold in each country is very large.

Numbers of flavoured products per brand/manufacture differ significantly, depending significantly on the type of organisation. In the US (2017) Tobacco Companies sold an average of 20.7 flavours, internet sources offered an average of 56.3 for sale, and Vape shops offered an average of 137.5 flavours for sale.

(iii) *Types of flavoured e-liquids sold:*

The names of flavoured e-liquids are extremely diverse, and range from the explicit (e.g., “tobacco”, “cherry”) to highly descriptive/abstract (e.g. “pursuit of sadness”, “Mad Murdock’s Radiator Fluid”). This has led Public Health Scientists to develop ways to understand and categorise flavoured e-liquids. Two major initiatives in this area were identified that provide internally consistent grouping rules and classifications:

Yingst *et al*⁽¹¹⁰⁾ focused on a hierarchical system with consistent with US societal definitions, and an emphasis on categories such as candy, dessert/sweet, alcohol, tobacco and an apparent strategy of minimising the numbers of flavours classified as tobacco or menthol in order to align e-liquid categories with US bans on flavoured tobacco cigarettes.

Krüsemann *et al* developed a more descriptive, non-hierarchical, e-liquid framework, “the flavour wheel”⁽¹¹¹⁾ which is consistent with categorisation approaches in other consumer goods industries. The resulting flavour wheel (below) contains 13 main categories and 90 subcategories. Tobacco and Mint categories are small subsets of the overall wheel. A set of explicit categorisation rules were also presented.

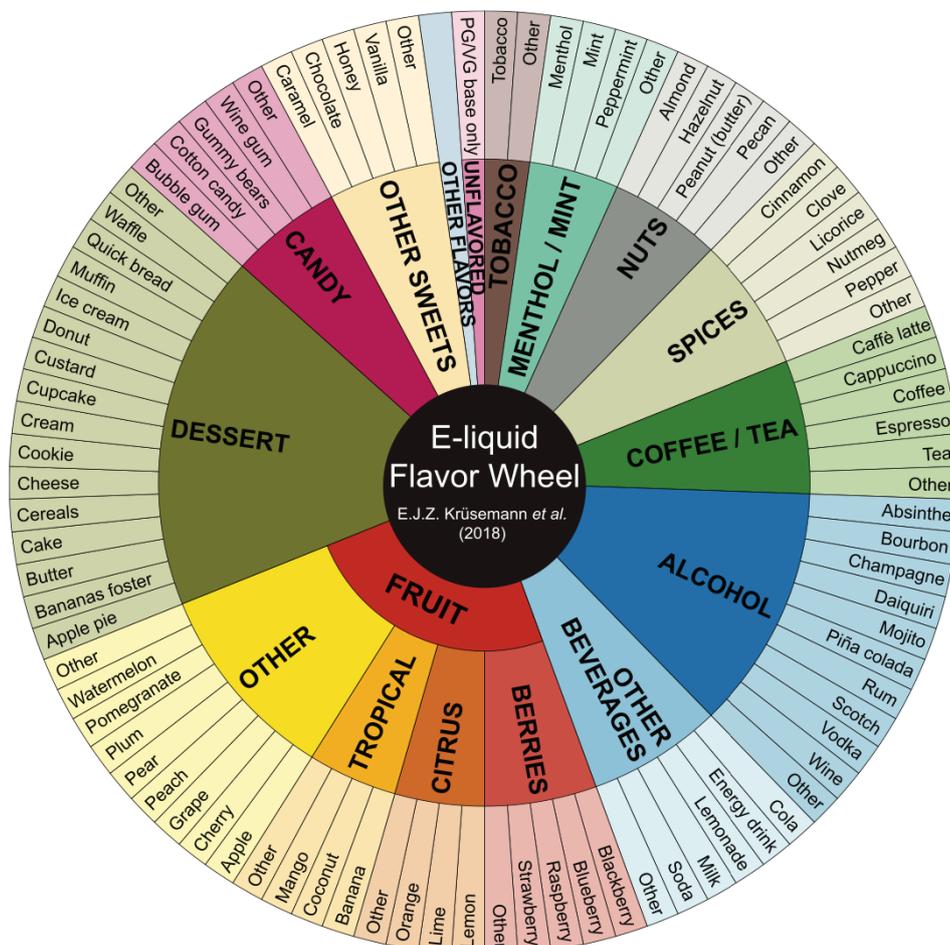


Table 3: E-liquid Flavor Wheel (E.J.Z. Krüsemann *et al*)

(iii) The most popular e-liquids:

Many published papers describe the relative preferences/sales of different flavoured e-liquids. Comparing the findings of these studies is not straightforward, as different studies use different categorisation approaches.

There are some indications of differences in preferences over time, and to some degree age, and geography. However, using the Flavor Wheel approach of Krussemann *et al*, the most prominent flavoured e-liquids available for sale in the Netherlands in 2017 were fruit (34%), tobacco (16%), dessert (10%) and mint (8%)⁽¹¹⁾. There was also evidence in this study that the percentage of e-liquids with high nicotine concentrations (18 mg/mL) was highest within the unflavoured category (40%)⁽¹¹⁾. Similar conclusions were reached in recent UK consumer surveys.

(iv) What are flavoured e-liquids composed of?

Most of an e-liquid is made up of the humectants vegetable glycerol (VG) and propylene glycol (PG), water and the reward-compound nicotine. The other compounds present in e-liquids are flavour ingredients. These are either artificial flavouring compounds, natural extracts such as fruit or plants, or synthetically made natural compounds (“nature-identical flavours”).



4. SMOKING CESSATION AND FLAVOURS

a. **Key link between (mostly flavoured) ENDS / nicotine vaping products and smoking cessation**

Key fact: Nicotine Replacement Therapies (NRT) are included in the World Health Organization List of Essential medicines

Cross-sectional surveys of (mostly flavoured) electronic cigarette users suggest that the main motivation for use is to reduce or quit smoking^(95,96,112,113). However, the study samples are not representative of the general population. Two studies of vape shops customers found that > 65% of electronic cigarette users had completely quit smoking^(114,115). Importantly, the smoking status was assessed in both studies by measuring exhaled carbon monoxide. Randomized controlled trials showed modest effects on smoking cessation for first-generation devices, and somewhat better results for newer-generation devices^(116–118). However, the products used in some of these studies were outdated and were already withdrawn from the market at the time of study completion or publication^(117,118). Two more recent randomized controlled trials clearly showed that electronic cigarettes were more effective than NRTs^(3,119). Some cohort studies have shown that electronic cigarettes increase the odds of quitting while others report no benefits^(120–125). However, many studies suffered from strong bias, mainly failure to examine whether participants were motivated to quit smoking and were using electronic cigarettes for smoking cessation, and unclear differentiation of participants according to frequency of electronic cigarette use. In some studies there was bias of the outcome being present at baseline, since many participants were recruited while they had already failed to quit smoking with the use of electronic cigarettes^(121,123). Several meta-analyses have also shown mixed results^(126–130). However, an updated Cochrane review report analysed 50 studies and concluded that there is moderate-certainty evidence that electronic cigarettes with nicotine increase quit rates compared to electronic cigarettes without nicotine and compared to NRTs⁽¹³¹⁾. A recent analysis of the 2017 Eurobarometer survey reported that, compared to never electronic cigarette use, daily use was associated with 5-fold higher odds of being a former smoker of ≤ 2 years (adjusted prevalence ratio: 4.96, 95% CI 3.57 to 6.90) and 3-fold higher odds of being a former smoker of 3-5 years (adjusted prevalence ratio: 3.20, 95% CI 2.10 to 4.87)⁽¹³²⁾. Even former electronic cigarette use was associated with higher odds of being a former smoker of ≤ 2 years compared to never e-reported that current electronic cigarette use was strongly associated with recent (≤ 12 months and 13-36 months) smoking cessation (ORs 6.12 and 6.28, respectively). For current daily electronic cigarette use, the association was even stronger OR: 10.41 for being a former smoker of ≤ 12 months and OR: 11.18 for being a former smoker of 13-36 months)⁽¹³³⁾.



The inherent problems of cohort studies and the limitations of randomized clinical trials, mainly the long duration for trial planning, recruitment, implementation and analysis⁽¹³⁴⁾, and the use of a single product compared to placebo, raise concerns about their applicability to electronic cigarettes. The use of electronic cigarettes as smoking substitutes represents a behavioural change, and product choice is based on self-reference⁽⁴⁴⁾. Despite randomized controlled trials being valuable in assessing the efficacy of electronic cigarettes in smoking cessation, their methodology needs to be adjusted by allowing for different product choice and being flexible in using different products (e.g., different flavours) during the trial.

Indirect evidence about the association between electronic cigarette use and changes in smoking status can be derived from population studies. The number of electronic cigarette users in the UK has grown from 700,000 in 2013 to 3.2 million in 2020⁽¹³⁵⁾. The majority of users were former smokers and the main reason for use was to quit smoking and to avoid relapse. In the European Union, approximately 6.1 million smokers reported quitting with the help of electronic cigarettes until 2014⁽⁴²⁾. Daily electronic cigarette users were far more likely to be former smokers compared to ever users^(31,136), which shows the importance of addressing regular use. A real-world assessment of the effectiveness of electronic cigarettes as a cessation aid reported 60% higher odds of quitting compared to over-the-counter NRTs⁽¹³⁷⁾. Obviously, such studies have important limitations, including the unknown temporal association and causality, self-report bias and subjective assessment of the smoking status and of the smoking cessation duration.

b. Role of (Flavoured) Medicinal Nicotine Replacement Therapy (NRT) in smoking cessation

There are some key questions in examining the role of medicinal nicotine replacement therapy (NRT) in smoking cessation:

- (i) What formulations of NRT are on the WHO's list of Essential Medicines?*
- (ii) Of the formulations of NRT that are approved by WHO, what percentage of the medicines consumed globally are flavoured?*
- (iii) Is there evidence to show that smokers are more likely to quit with the help of flavoured NRT?*
- (iv) Does flavoured NRT have a higher abuse liability than non-flavoured NRT?*

(i) *WHO list of essential medicines*

Table 4: Excerpt from the WHO's list of essential medicines 2021⁽¹³⁸⁾

24.5 Medicines for disorders due to psychoactive substance use	
bupropion	Tablet (sustained-release): 150 mg (hydrochloride)
nicotine replacement therapy (NRT)	Chewing gum: 2 mg; 4 mg (as polacrilex). Transdermal patch: 5 mg to 30 mg/16 hrs; 7 mg to 21 mg/24 hrs.
varenicline	Tablet: 0.5 mg, 1 mg

Note that whilst nicotine gum and patches are listed as essential medicines, electronic nicotine delivery systems (ENDS) and oral nicotine pouch formulations are not. This is particularly interesting given the results of a randomised control trial in 2019 by Hajek et al, which found that in a sample of 886 participants, those randomised to the e-cigarette group were 1.83-fold more likely to have quit smoking than those in the NRT group (who could choose one or more of: patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouth strip, and microtabs)⁽³⁾

(ii) *Flavoured NRT*

The global market share of each type of NRT in 2020 is as follows⁽²⁾:

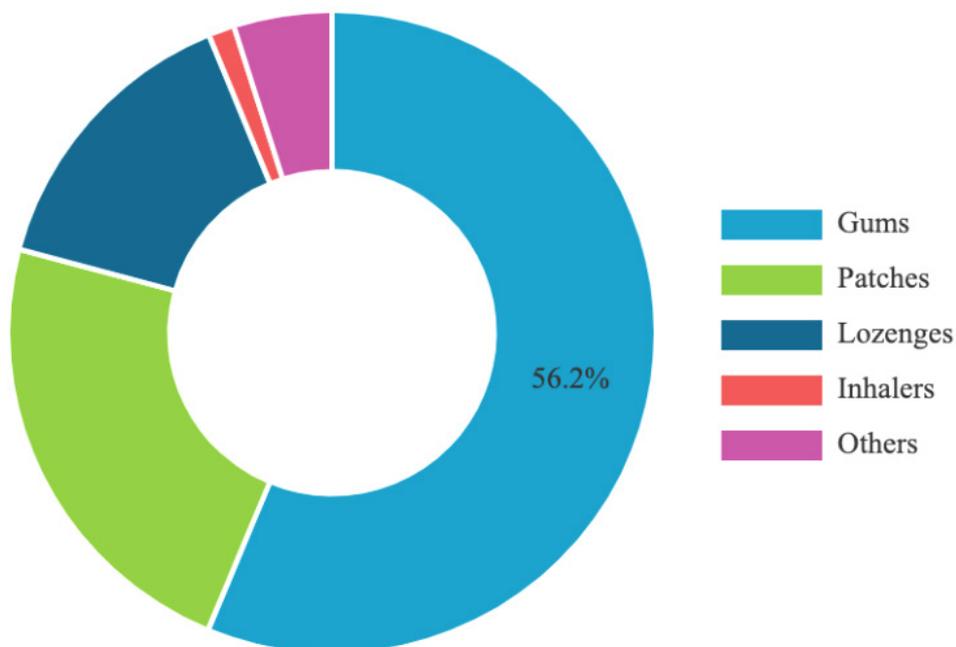


Table 5: Global Nicotine Replacement Therapy Market Share, by type, 2020⁽²⁾

Nicotine gum, at 56.2% of the global market share, is the most used form of NRT. It is difficult to find publicly available data that categorises NRT market share by flavour. But there is a wide assortment of available flavours: mint (many variations thereof), fruit, cinnamon, unflavoured, etc.

(iii) Are smokers more likely to quit with flavoured NRT?

Following a basic scoping review, there have been no RCTs directly comparing acceptability and efficacy of flavoured vs non-flavoured NRT (gums, lozenges, sprays). There was, however, a German RCT comparing new flavours to older ones. In 2011, Von Mulzer et al compared consumer acceptance of two new flavoured nicotine gums versus older existing nicotine gums⁽¹⁴⁰⁾. In one group, a new fruit-flavoured nicotine gum (A) was compared with an existing flavour (B). The percentage of participants who rated flavour A “just right” was ‘significantly higher’ than in flavour B. Similarly, in another group, new mint-flavoured gum (N) was compared with existing mint flavours (M and Q). With regard to consumer perception of which gum would be more likely to help quit smoking, ‘significantly more’ participants expressed greater confidence in new flavour N than older M and Q.

Although there is a paucity of trial evidence comparing flavoured vs non-flavoured NRT, it should be noted that flavours are used for the very purpose of making them more appealing to adult smokers, and therefore more efficacious in helping them quit⁽¹⁴¹⁾. Surely, the same reasoning must therefore apply to ENDS and oral nicotine, which is currently held in disregard by the WHO.

Furthermore, to highlight a study by Posner et al from 2021 – 2159 young US adults were interviewed regarding the impact of sales restrictions on flavoured e-cigarette products. If flavours were restricted to tobacco flavours only, 33.2% of e-cigarette users reported being likely (very/somewhat) to relapse back to cigarettes. If e-cigarettes were totally banned, 39% reported they would return to smoking⁽¹⁴²⁾.

(iv) Does flavoured (smoke-free) nicotine products have a higher abuse liability than non-flavoured (smoke-free) nicotine products?

In 2020, Goldensen et al assessed the abuse liability of the JUUL system in four flavours (Virginia Tobacco, Mango, Mint, and Creme) compared to combustible cigarettes, nicotine gum (mint), and a comparator e-cigarette (VUSE Solo; tobacco flavour)⁽¹⁴³⁾. In a sample of 66 adult smokers, nicotine pharmacokinetics were compared in controlled conditions for all the above products.

Combustible cigarettes were significantly highest in:

- Maximum plasma nicotine level
- Rate of plasma nicotine rise
- Overall nicotine exposure
- Subjective liking and satisfaction

However, the JUUL system and ENDS (e-cigarette) Comparator (Vuse) were higher in all of the above parameters compared to nicotine gum. Of note, the Mint and Mango flavours were rated as more satisfying than Virginia Tobacco and Creme. The authors of the study concluded that product liking, and satisfaction were higher in the ENDS (e-cigarette) group than the nicotine gum group, but that it had higher abuse liability due to the greater nicotine exposure. Nonetheless, ENDS was shown to provide sufficient nicotine delivery to support substitution of combustible cigarettes among adult smokers⁽¹⁴³⁾.

5. SCIENCE DIMENSION OF FLAVOURS USED IN ENDS / NICOTINE VAPING PRODUCTS

In examining the scientific basis for flavours, it is essential to first consider the science underpinning the other elements of nicotine vaping products and its impact on individual and population health. It is well-established that smoking causes disease after long-term use. Therefore, long term epidemiological follow-up is needed to determine the clinical effects of electronic cigarettes and the change in disease risk compared to smoking. Additionally, the past smoking history of electronic cigarette users would need to be taken into consideration. With electronic cigarettes being widely available for only 10-12 years, it is not surprising that long-term epidemiological studies are scarce. Still, there is extensive preclinical research, examining the chemical and toxicological profile of these products.

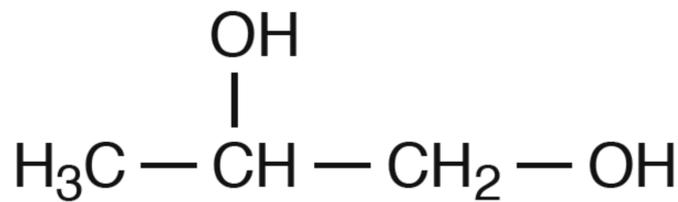
a. ENDS / Nicotine Vaping Products chemistry

Tobacco cigarette smoke contains thousands of chemicals, many of which have established toxic and carcinogenic potential⁽¹⁴⁴⁻¹⁴⁶⁾. Many of these compounds are products of combustion, but some are also present in tobacco, especially cured tobacco⁽¹⁴⁷⁻¹⁵¹⁾. The combustion process is the main determinant of toxic emissions. In tobacco cigarettes, temperatures of up to 900oC at the burning tip have been observed⁽¹⁵²⁾. Inorganic compounds, such as heavy metals, are also emitted. Exposure to the compounds cause disease mainly through inflammation, DNA damage and oxidative stress⁽¹⁵³⁻¹⁵⁷⁾.

The main difference between electronic cigarettes and tobacco cigarettes is the lack of combustion in the former. This provides insight about the potential risk differences between the two products. In electronic cigarettes, liquid is being evaporated and then recondensed into an aerosol which is inhaled by the user. Additionally, the liquids ingredients are compounds which have been used for years in human consumption products such as food, cosmetic and pharmaceutical products. In fact, all ingredients of electronic cigarettes are derived from the food, pharmaceutical and fragrance industry. The main ingredients, besides nicotine, are propylene glycol, glycerol and flavourings.

(i) *Propylene glycol*

Propylene glycol was first developed by Charles-Adolphe Wurtz in 1859⁽¹⁵⁸⁾. For commercial use, it is produced from propylene oxide by hydrolysis. Propylene glycol is mostly used in producing unsaturated polyester resins⁽¹⁶⁰⁾. It is also used to generate artificial mist and fog, with applications in fire safety training and in theatrical productions⁽¹⁶¹⁾. Since its approval by the FDA in 1982, it has been used



Propylene glycol (1,2-propanediol)

Table 6: Chemical structure of propylene glycol.

in food, pharmaceutical products and tobacco. It is also Generally Recognized As Safe (GRAS) and can be added to food products⁽¹⁶²⁾. Some oral and intravenous medications also contain propylene glycol, such as diazepam, lorazepam, and phenobarbital⁽¹⁶³⁾. It can also be used through inhalation and has been used as an excipient for inhaled immunosuppressive medications^(164–166). Pharmaceutical grade propylene glycol should be $\geq 99.5\%$ pure, should contain ≤ 5 ppm heavy metals and $\leq 0.2\%$ water, and its specific gravity is 1.035-1.040. No impurities such as diethylene and ethylene glycol should be present at levels $> 0.10\%$.

Dermal contact from cosmetic products and oral exposure through use in food, tobacco and pharmaceutical products are the commonest type of exposure for humans. In the United States, the average consumption per person was estimated at 34.3mg per kg body weight per day (approximately 2.4g)⁽¹⁶⁷⁾. In Japan, the average daily intake was estimated at 43 mg per person per day⁽¹⁶⁸⁾. Occupational exposure and intravenous administration through medications are less common exposure routes^(163,167). The US Occupational Safety and Health Administration (OSHA) or the American Conference of Governmental Industrial Hygienists (ACGIH) have not established any safety exposure levels for propylene glycol inhalation. An inhalation aerosol exposure safety limit of 10 mg/m³ has been set by the American Industrial Hygiene Association (AIHA)⁽¹⁶⁹⁾.

In the human body, propylene glycol is oxidized to lactaldehyde and then to lactate^(169–171). Propylene glycol is excreted by the kidneys, either unchanged or as a glucuronic acid conjugate, with a half-life of 2-4 hours^(172,173). It is toxic to cats⁽¹⁵⁵⁾. There is no evidence for carcinogenicity in humans, while local skin irritation from propylene glycol patches has been reported⁽¹⁷⁴⁾. In adults, toxicity is observed only at very high serum levels⁽¹⁷²⁾. It is mainly expressed as seizures, especially in children^(175–177). Lactic acidosis is an infrequent toxic effect, which has been reported after intravenous administration of medications^(178–181).

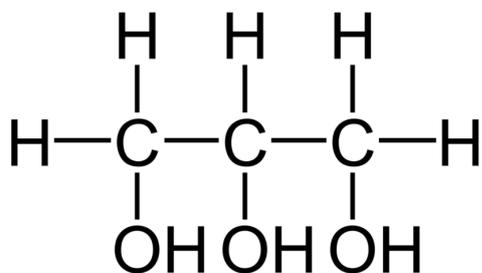
Propylene glycol is an excellent solvent for electronic cigarette liquids and has been used since electronic cigarettes were invented⁽¹⁸²⁾. Its aerosolization results in the production of visible aerosol resembling “smoke”. It also causes throat

irritation (“throat hit”) which is a desirable sensation for both smokers and electronic cigarette users unless it is excessive^(112,182–184). Propylene glycol produces less visible aerosol than glycerol but stronger throat hit⁽¹⁸⁵⁾.

Exposure to propylene glycol from electronic cigarette occurs via inhalation, which is a novel exposure route. Studies examining the safety of propylene glycol vapours were performed in the 1940s, due to findings that propylene glycol aerosol had bactericidal and virostatic properties observed in animals^(186–188). Similar protective effect was found in humans^(189,190). A research group led by Prof. Robertson from the University of Chicago performed research propylene glycol aerosol^(191–193). They exposed rats and monkeys to environment saturated with propylene glycol vapours for 12 to 18 months and found no toxicity on any organ⁽¹⁹⁴⁾. An animal study performed in 1989 found minimal irritating effects in the nasal cavity, probably due to tissue dehydration⁽¹⁹⁵⁾. Another study examined the effects of propylene glycol mist exposure used from its use in aircraft de-icing. Twenty-seven subjects were recruited, with more than half of them being smokers (current or former)⁽¹⁹⁶⁾. Spirometry was used to examine lung function changes after 1 minute of exposure to 309 mg/m³ propylene glycol concentration, and irritating symptoms was assessed through a questionnaire. Mild eye irritation was observed. A marginally significant decrease of FEV1/FVC (p=0.049) was also observed, which was due to an increase in FVC. However, increased FVC is not observed in any lung disease⁽¹⁹⁷⁾. Still, it is important to mention that electronic cigarettes will result in higher duration of exposure to inhaled propylene glycol compared to workers in de-icing.

(ii) *Glycerol*

Glycerol (also called 1,2,3-propanetriol) is a polyol (Table 7). It is a natural occurring substance which is viscous, colourless and odourless, and has a sweet flavour. It is a humectant. It is miscible with water and alcohol. Its boiling point is 290°C and its freezing point is 17°C⁽¹⁹⁸⁾.



Glycerol(1,2,3-propanetriol)

Table 7: Chemical structure of glycerol.

Glycerol is necessary for the formation of triglycerides⁽¹⁹⁹⁾. Thus, it is essential for living organisms, including humans, animals and plants. It was obtained by heating fats in the presence of ash to produce soap as early as 2800 BC⁽²⁰⁰⁾. It was accidentally discovered in 1779 while heating a mixture of olive oil and lead monoxide⁽²⁰¹⁾. Glycerol became important when it was used in the manufacturing of nitro-glycerine, and became a military resource after Alfred Nobel discovered nitro-glycerine use as an explosive (dynamite). During the First World War, high demand led to the development of plants to synthetically produce glycerol⁽²⁰²⁾. The US annual production capacity was approximately 350,000 tons in the early 2000s⁽²⁰³⁾. The worldwide production is estimated at 2 million tons annually, mainly coming from the growing biodiesel industry⁽²⁰³⁾.

Glycerol is used in pharmaceuticals, food, cosmetics, tobacco, and in paints, resins and paper⁽²⁰⁴⁾. It was classified as GRAS in 1959. In the form of monoglycerides, it is used as a stabilizer and emulsifier⁽²⁰¹⁾. Pharmaceutical grade glycerol specifications include having $\geq 98.0\%$ purity and containing ≤ 5 ppm heavy metals ≤ 2.0 to 5.0% water, ≤ 10 ppm aldehydes and ≤ 10 ppm chlorides⁽²⁰⁵⁾.

Glycerol is rapidly absorbed in the stomach and intestine, and it is distributed to the extracellular space⁽²⁰⁶⁾. It is transformed to alpha-glycerophosphate by glycerol kinase, mostly in the liver and kidneys. It is then introduced into standard metabolic pathways and is transformed to glucose and glycogen^(206,207). It also forms triglycerides in the liver, together with fatty acids, a process that depends on glycerol levels in plasma⁽²⁰⁸⁾.

Glycerol inhalation may occur to aerosols released from the spray application of resins or paints⁽²⁰⁴⁾. The OSHA Permissible Exposure Limit (PEL) for glycerol mist inhalation is 5 mg/m³ for the respirable fraction⁽²⁰⁹⁾. ACGIH has established a TLV of 10 mg/m³. Oral doses of ≤ 1.5 g/kg are easily tolerated, causing slight diuresis only. In rats, the oral LD50 value is >24 g/kg^(210,211). The oral LD50 values in guinea pigs and mice are 10 and 23 g/kg, respectively⁽²¹⁰⁾. A single LD50 of >18 g/kg for acute dermal toxicity for rabbits has been established⁽²¹⁰⁾. No skin or eye irritation has been reported⁽²¹¹⁾. No toxic effects were identified when administered intravenously in humans⁽²¹²⁾, while one study found elevated triglyceride levels after chronic oral intake⁽²¹³⁾.

In electronic cigarettes, glycerol is used as a solvent. It also produces thick and visible aerosol, thicker than propylene glycol. It appears to cause milder throat hit compared to propylene glycol, thus it is used as a solvent in low-nicotine liquids used for a specific pattern of electronic cigarette use called "direct lung inhalation" (the user inhales the aerosol from the atomizer directly into the lungs). A study of glycerol inhalation in rats identified metaplastic changes in the epiglottis epithelium, but no adverse effects in the lungs or other organs⁽²¹⁴⁾.

b. Safety studies of flavoured e-liquids (used in ENDS)

After a basic review of relevant articles, some observations for consideration and future research:

(i) Examining the suitability of flavours for inhalation:

Many authors have noted that most flavouring materials used in e-liquids are designated as generally recognized as safe (also known as GRAS) by FDA. This is a term that has grown out of the food industry, and the GRAS status refers specifically to ingestion. The GRAS principle, combined with the knowledge/experience/familiarity of flavourists appears to be the basic level of product stewardship that has existed in much of the industry⁽⁹⁹⁾.

However, most of these flavour compounds were never studied for toxicity via the inhalation route. The respiratory tract is generally much more sensitive to chemical agents than those in the gastro-intestinal tract, and different disease mechanisms can operate. There is some additional support for the safe use of some flavour ingredients from dermal exposure studies. However, repeatedly, concerns have been expressed in Public Health that these GRAS flavour ingredients have not been widely tested for respiratory safety concerns such as sensitisation, respiratory toxicity, or irritating potency, and therefore the potential exists for respiratory health effects following long-term exposure.

As is common practice in the food and beverage industry, manufacturers of nicotine vaping products should be obligated to introduce more thorough product stewardship approaches and strategies, as has been pointed out by the UK Committee on Toxicology (COT) in 2020: "To ensure toxicological risks are kept to a minimum, the Committee emphasises the need for good production standards for E(N)NDS products. (...) For e-liquids, the formulants should be derived from a reputable source, and non-standard constituents should not be included."⁽²¹⁵⁾

(ii) Chemical impurities in flavours and reaction to by-products:

Natural extracts have been shown to contain impurities or other ingredients that might not contribute to the flavouring properties of the end-product, including metals, which might raise safety concerns. Furthermore, flavour ingredients, and the main e-liquid constituents are not chemically inert⁽²¹⁶⁾. Further studies are needed to confirm how flavour ingredients can react with PG, VG or nicotine in the e-liquid to form new compounds and whether there are measurable toxicological properties.

(iii) Thermal degradation products:

When heated in the e-cigarette atomiser, flavour ingredients can break down into a range of separate compounds. In several of my own studies, we have studied whether flavouring compounds contribute to aldehyde emissions in e-cigarettes⁽²¹⁷⁾. We found that the e-cigarettes tested herein emit very low levels of aldehydes. Some flavourings may contribute to aldehyde emissions, but the absolute levels were minimal⁽²¹⁷⁻²¹⁹⁾. It is important that validated methods are used when analysing e-cigarette emissions.

Some studies have suggested that flavour ingredients might generate carbonyls, and it has been suggested that they are the source of carbonyls in e-cigarette aerosols⁽²¹⁸⁾. However, these findings have been challenged by replication studies showing that the contribution of flavouring compounds to the formation and emission of carbonyls is far lower than previously observed⁽²¹⁷⁻²¹⁹⁾.

(iv) Safety – in vitro studies

Mechanisms of e-cigarette toxicity have been investigated in many studies by exposing different cell types directly to e-cigarette liquids. Recent high-throughput technology improvements have enabled screens of large e-liquid libraries. Studies are increasingly focusing on cell-aerosol exposures. The toxicity data reported from these studies are a function of how the cells are exposed, which cell types, product operating parameters and e-liquid content (including flavours). The predominant toxicity effects reported include cell viability and cytotoxicity, oxidative stress and inflammation, barrier and membrane dysfunction, genotoxicity and DNA damage.

Recognition of these potential issues has led to the widely expressed view that research on the presence and effects of inhaled flavourings is warranted, and many studies are underway to this end. However, many of the studies to date have used questionable dose and exposure conditions; several studies have concerns associated with the appropriateness of the models; necessary comparators such as cigarette smoke are often missing from the studies. These views were raised by the Committee on Toxicity of the UK government (COT) amongst others⁽²¹⁵⁾, and to-date the findings of many of these studies should be viewed with caution.

(v) Safety – animal studies:

There have been a series of studies on the toxicities of flavoured e-liquids and flavour ingredients in animals. The latest research on effects of ENDS use might suggest some short- and long-term toxicities from inhaling aerosols of glycerol, propylene glycol, nicotine, and flavouring materials. Exposure of

different animal models to ENDS products via various routes of exposure can be used to inform the potential for adverse health outcomes resulting from ENDS usage. However, the complex nature of e-liquids makes it difficult to identify which ingredients, or their potential synergistic effects, are harmful.

Questions have also been raised about the appropriateness of the conditions used in many of these studies, with unrealistic doses, duration of exposure, and mechanism of action. Translation of these findings to human conditions relevant to consumers is a complex procedure.

(vi) Safety - Populations Studies:

The 2020 SCHEER report⁽²²⁰⁾ concluded that the evidence available to date showed individual and interactive effects of flavour and additives used in electronic cigarettes collectively and detrimentally impact cardiovascular health, including the propagation of increased heart rate and increased diastolic blood pressure, posing users at elevated subsequent risk for manifesting cardiovascular disease (CVD). The SCHEER report also concluded that several investigations corroborated that electronic cigarette use induces DNA damage via increased oxidative stress, with most profound effects being associated with flavoured e-liquid use. A number of flaws have been pointed out in this report, including the paucity of quality vaping studies. For example, Public Health England (PHE) commented:

“The methodology was not reported in sufficient detail in the report or annex to be able to understand how the evidence summarised had been selected. Established guidelines for systematically reviewing evidence and the reporting of reviews had not been followed. For example, search terms given for the review i) did not capture all of the questions covered in the opinion; ii) had a start date of January 2015 and hence included studies of vaping products marketed long before the TPD was in place and iii) had a cut-off of April 2019 which was 18 months before the publication of the preliminary opinion and hence a reliance on out-of-date data in this quickly moving field. The report included predominantly US studies which therefore involved products which were regulated very differently from the TPD regulations. There was also no information on the quality of the studies included.”⁽⁵⁾

Nevertheless, SCHEER concluded that the long-term health effects of electronic cigarettes remain for the most part unknown to date, and further investigations are urgently needed regarding their impacts upon both pulmonary and other health systems.

c. Social & Behavioural Sciences: Surveys and Usage Patterns

(i) Largest Survey ever on (Flavoured) ENDS use in the USA

During 2016, Chris Russell and I performed, what was to date the largest ever survey on e-cigarette use in terms of sample size, with almost 70,000 participants in the United States of America⁽⁹⁸⁾.

The main findings of the study were that non-tobacco flavours, especially fruit and dessert/pastry/bakery flavours, were the most prevalent choices among adult, established, dedicated US e-cigarette users who participated in the study. They were particularly popular not only during long-term e-cigarette use but also at the period of e-cigarette use initiation.

Additionally, these flavours were very popular among former smokers who were using e- cigarettes at the time of smoking cessation. Fruit and dessert/pastry/bakery flavours were also considered particularly important in their effort to quit smoking and to prevent relapse to smoking. Tobacco flavours were generally used by a minority of the study participants, and their use prevalence decreased substantially over time. The patterns of e-cigarette flavours use observed in that study were in agreement with another cross-sectional study examining the responses of more than 20,000 participants from the US ⁽²²¹⁾.

Since the regulation on e-cigarette flavours should consider the balance between protecting from unintended use (e.g., by adolescents or never smokers) and avoiding adverse effects and potential harm (e.g., by preventing smokers from switching to e- cigarettes in a harm reduction approach to quitting smoking), we hope regulatory bodies will find the data presented in these studies useful in preparing the appropriate regulatory framework. The data raise the possibility that an overly restrictive regulation, such as banning the sales of specific flavour groups (especially fruit and dessert/pastry/bakery flavours), might prevent smokers from switching to e-cigarette use or may increase the relapse rate among former smokers who have managed to quit with the help of e-cigarettes⁽²²²⁾.

A major limitation of the study⁽⁹⁸⁾ is the cross-sectional design and the recruitment of a convenience sample of dedicated e-cigarette users. The sample is not representative of the general US adult population and the study was not designed or intended to estimate the prevalence or frequency of e-cigarette flavours use. The flavour preferences and patterns of e-cigarette use reported by the present sample of dedicated e-cigarette users may more closely represent those of the 21.3% of current e-cigarette users in the USA who use e-cigarettes daily and not the majority who are infrequent users or experimenters⁽²²³⁾. Still, this survey presents the patterns of use of a very large sample of adult US e-cigarette users, most of which self-reported that they were

successful in quitting smoking with the help of e-cigarettes. While flavours seem to play an important role in their smoking cessation attempt, it should be mentioned that other characteristics, such as the more prevalent use of advanced e-cigarette devices compared to ciga-likes, may also contribute to a successful quit attempt⁽²²⁴⁾.

In conclusion, this cross-sectional study of a very large sample of adult US e-cigarette users⁽⁹⁸⁾, most of which were former smokers, identified the importance of non-tobacco flavours in e-cigarette use initiation and sustained use, and their contribution to smoking cessation and relapse prevention. This information should be considered by regulators in order to avoid unintentional adverse effects of over-restrictive regulation on e-cigarette flavours.

(ii) Impact of flavours on usage patterns

A substantial increase in the prevalence of e-cigarette use has been observed worldwide in recent years, amongst both adults and youth, although use levels are heterogeneous across the globe⁽⁴⁾.

In the USA increased youth vaping has become a major concern, due to the perceived risk that e-cigarettes may introduce a wider, younger population to nicotine addiction, and debatable concerns that they may act as a gateway to cigarette smoking and may cause harm to developing brains⁽²²⁵⁾. Adolescents have been consistently reported to be associated with comparatively higher rates of using e-cigarettes containing characterizing flavours, and a consistently lower use of tobacco-flavoured products⁽²²⁶⁾.

The term 'characterizing' flavour, used frequently in this area, is defined as a 'clearly noticeable smell or taste other than one of tobacco, resulting from an additive or a combination of additives, including, but not limited to, fruit, spice, herb, alcohol, or candy which is noticeable before or during the consumption of the tobacco product'⁽²²⁷⁾.

- **Perceived flavour safety:**

Across all age groups characterizing flavoured products are perceived as less harmful than tobacco flavours; but this is particularly pronounced in younger populations^(98,221,226,228).

- **Flavour Preferences:**

Flavours also offer users a means of customizing their products and increase opportunities for experimentation, both of which are cited as important reasons for youth e-cigarette use^(221,226). E-cigarettes with characterizing fla-

vours are consistently rated as sweeter than those with menthol or tobacco flavouring, and it is common among “Do-It-Yourself” users to add sweeteners to their e-liquids⁽²²⁹⁾. Young people have strong and disproportionate innate preferences for sweetness (that diminish with age) which may consequently increase use⁽²³⁰⁾.

On a broader basis, research suggests that men are more likely to use e-cigarettes, but women are slightly more likely to use characterizing flavoured products and/or to value flavour availability. Characterizing flavours might also attract specific (and potentially vulnerable) populations⁽²³¹⁾.

- [Effect of flavours on reward, reinforcement and consumption](#)

There is evidence that characterizing flavours affect nicotine reward, reinforcement, and consumption⁽²³¹⁾. An interesting observation is that characterizing-flavour e-cigarettes appear to be rewarding even in the absence of nicotine, with studies reporting significant numbers of adolescents vaping “just flavour”⁽²³²⁾. Flavour chemicals are not inert, and some have intrinsic pharmacological effects such as monoamine oxidase (MAO) inhibitor activity, which can increase nicotine reward in rodents⁽²³³⁾. For example, vanillin inhibits MAO activity much more potently than harman, one of the major MAO inhibitors found in tobacco smoke. In rats, high doses of linalool can alter the activity of enzymes that are responsible for nicotine metabolism⁽²³³⁾. These observations have led to suggestions that if characterizing flavours are intrinsically rewarding, then ‘flavour reward’ and ‘nicotine reward’ could interact in some way to make vaping flavoured products more reinforcing and thereby potentially increase total nicotine consumption⁽²³¹⁾.

- [Effect of flavours on intake and uptake](#)

A small number of studies have found that flavours influence puffing topography, rate of nicotine absorption and increases in participants’ heart rate amongst vapers^(234,235). Clinical reports have shown that characterizing flavours can increase nicotine consumption, as measured by an increase in the number of puffs taken, increased volume of e-liquid used, and longer duration of ‘puffs’ during ad libitum vaping sessions^(233,234). A sensory mechanism has also been proposed where menthol and potentially other characterizing flavours could alter nicotine salience is by ‘masking its harshness’, making e-cigarettes more appealing to younger consumers⁽²³¹⁾. The rate of drug delivery to the brain is correlated with strength of reward and reinforcement⁽²³⁶⁾. Differences in e-liquid acidity has been proposed as a potential mechanism for flavour-mediated increases in the rate of nicotine absorption, analogous to protonation⁽²³⁷⁾. This would suggest that more acidic liquids in general might share this property,

which was noted as potentially having important implications on the abuse liability of certain e-cigarette products^(231,237,238).

- **Flavour preferences amongst youth**

Characterizing flavours in nicotine products are thought to have age-specific effects⁽²³¹⁾. Initially, this led to a concern that characterizing flavours were only popular with young e-cigarette users and served to attract adolescents disproportionately toward nicotine use⁽²²⁵⁾. However, adults are now increasingly using flavoured e-cigarettes^(98,221). Despite universal popularity of characterizing flavours, adolescents and young adults are regarded as more interested in and to have greater intentions to try flavoured tobacco products than adults⁽²²⁸⁾.

It is now widely posited therefore that use/availability of characterizing flavours are a significant factor in the increase of adolescent e-cigarette use in recent years^(226,232). A balancing argument is that flavoured e-cigarettes attract only the subset of adolescents who were already susceptible to tobacco use or are 'high sensation seekers'⁽²²⁸⁾.

- **Effect of flavours on combustible product use:**

A further concern amongst some public health scientists is that the increase in flavoured e-cigarette uptake will lead to increased combustible cigarette use over time, i.e., the gateway effect⁽²³⁹⁾. The rationale is that if adolescents initiate with flavoured e-cigarettes, their first exposure to nicotine is more likely to be pleasant, and individuals who report a positive first experience with smoking are more likely to go on to become regular smokers. However, not all research suggests that flavours are associated with a progression to combustible use, and therefore, the role of flavoured e-cigarettes on the ability to cause progression to combustible cigarettes is still unclear^(228,231,239,240).

These concerns, over the hazards that characterising flavours may pose to youth, have led to widespread calls by some public health researchers that e-cigarette flavours should be banned to reverse the observed trends in youth e-cigarette and nicotine consumption⁽²⁴¹⁾. However, in practice, a flavour ban in 2019 in San Francisco had unintentionally harmful consequences – most notably, an increase youth combustible cigarette use⁽⁹⁾.

- **Effect of flavours on smoking cessation:**

By way of contrast, in adults, while flavours may lead to increased e-cigarette consumption^(228,230,234,237), several reports suggest that it is also associated with decreased combustible cigarette use and can serve to improve quitting rates amongst established smokers^(7,8,94,98,127,128,131,133,242,243). Flavoured e-cigarettes there-



fore have the potential to reduce harm in adult smoking populations^(29,126,127,131). A repeated quandary that flavours present to public health experts is how to balance their possible efficacy in helping adult smokers to quit with the risks that characterising flavours may pose to youth⁽²⁴⁴⁾.

6. PUBLIC HEALTH DIMENSION:

What Public Health Experts Says about Flavours in ENDS / Nicotine Vaping Products

During 2021, there were several key consultations held by governments, as they contemplated the regulation of flavours used in products such as ENDS / nicotine vaping products. Below I have attached some of the key submissions to these governments, which act as an excellent summary of the views of world-class experts on the topic of flavours used in THR in general, and nicotine vaping products.

a. **Netherlands Government: Decree of the State Secretary for Health, Welfare and Sport on the Regulation of e-cigarette flavours in the Netherlands (February 2021)**

Twenty-four independent scientists and public health experts provided a comprehensive reply to the Dutch Ministry, the link to the submission can be found here ([Expert Response to Netherlands Flavour Ban](#))⁽²⁴⁵⁾ and I have attached the summary below:

Summary of Comments:

The case for the ban on vaping flavours described in the memorandum supporting the measure is wholly inadequate, and the measure should not proceed on this basis. The critical weaknesses in the rationale described in the memorandum are as follows:

1. Sets conflicting objectives and takes a “war on drugs” approach to nicotine.

The proposed measure is supposed to support a “smoke-free Netherlands” objective for 2040 as part of the Prevention Agreement. As stated, this is a sensible goal and should be widely supported – it recognises that *smoke*, not nicotine, is the overwhelming cause of disease. It is practical and achievable if smoke-free alternatives to smoking, such as vaping products, are available. However, the proposal introduces a significant expansion of scope by extending “smoke-free” to mean all tobacco, even if not smoked and then to tobacco-free nicotine products like e-cigarettes. It will make it impossible to use harm-reduction approaches, despite the enormous potential to reduce disease and death. It misunderstands the nature of youth risk behaviours. It amounts to extending the war on drugs to nicotine, but at a time when failures of prohibition are widely recognised. It would be better to stick to a smoke-free goal and use smoke-free alternatives to achieve it rather than pursue nicotine prohibition. The Netherlands is rightly world-famous for its pragmatic approach to soft drugs — that pragmatism should be leveraged to accelerate the end of smoking in the Netherlands by embracing harm reduction for those who smoke.

- 2. Adopts false and misleading claims about the risks of e-cigarettes.** The justification fails to adequately characterise the overwhelming evidence showing e-cigarette use is much less harmful than smoking^(2,5,51). Suppose policymakers believe e-cigarettes are just as harmful as cigarettes. In that case, their policies will be detrimental to public health by hindering substitution as smokers move from high-risk to low-risk products. It is clear from toxicology and exposure studies that e-cigarettes are, beyond any reasonable doubt, far less harmful than cigarettes. It is simplistic to apply the precautionary principle to use long-term uncertainties to justify excessive regulation. This ignores the substantial body of science suggesting much lower risk and neglects the problem that excessive regulation can cause harm by protecting the cigarette trade, which is known to be highly harmful.
- 3. Draws on irrelevant information about an outbreak of lung injuries in North America.** Without a credible case for harm arising from e-cigarette use, the justification includes distracting and irrelevant references to “EVALI”, an outbreak of severe lung injuries in the United States in 2019. EVALI was caused by the addition of a cutting agent, Vitamin E Acetate, to illicit *cannabinoid* (THC) vape pens⁽²⁴⁶⁾. This substance cannot be added to nicotine liquids and would serve no purpose if it could. There is no other credible evidence of material risks of severe lung injury.
- 4. Misunderstands “dual-use”.** Concurrent use of e-cigarettes and cigarettes (“dual-use”) should be understood as progress towards reducing smoking or smoking abstinence in most cases. Unless a smoking cessation method is 100% and immediately effective, it will mean some continued smoking on the pathway to smoke free status *whatever method is used*. It is true that some ‘dual users’ do not see significant reductions in toxicant exposure, but that is likely caused by higher dependence for which dual use is a marker. It is likely that public hostility to e-cigarettes, including from the government, agencies and academics, contributes to users not appreciating the benefits of switching completely. A cause of dual-use-related harm could, in part, be negative statements of tobacco control activists, academics and politicians.
- 5. Asserts a “gateway effect” but there is more likely to be a diversion away from smoking.** The memorandum claims there is a gateway effect from vaping to smoking. At an individual level, some adolescents will be likely to take up e-cigarette use, but there is also growing evidence that other adolescents who would otherwise have smoked are diverted away from starting to smoke. This diversionary effect is consistent with observed declines in youth smoking prevalence despite the recent increases in e-cigarette use as the technology has emerged. The strong correlations between smoking and vaping commonly reported in the literature are likely partly caused by

'common liabilities. These are characteristics such as genetics, mental health status, home environment, community, school etc. that incline a young person both to smoking and to vaping. *The vaping cannot be assumed to cause the smoking.* Regulating based on assumptions of a gateway effect where none exists is not responsible or 'precautionary'. Over-regulation of e-cigarettes, the far safer product, could prevent e-cigarettes functioning as a diversion from smoking for young people^(9,222).

6. Takes a simplistic approach to youth risk behaviours and fails to demonstrate benefits to adolescent public health.

The rationale offered is grounded in a naïve account of youth risk behaviours, which do not stop simply because adults in authority disapprove of them or pass laws to prevent them. There is a long and complicated chain of causation from a ban on e-cigarette flavours to improved health, with many possible diversions into perverse and harmful consequences. Legislating to ban something does not make it go away or necessarily cause its existing users to become abstinent – it provokes a variety of responses on the part of consumers. Illicit drugs are subject to prohibitions and strong sanctions yet are still widely used and supplied by criminal enterprise. The proposal lacks justification of the measure as a successful youth-orientated public health intervention. Without realistic insights into youth risk behaviours, the government is likely to regulate in a way that *increases* harm to young people – for example, by tacitly encouraging young people to revert to smoking.

7. Ignores perverse consequences of prohibition, even though these are foreseeable.

The case provides little analysis of a range of harmful perverse consequences that could arise from a prohibition of vaping flavours. These are foreseeable, yet not foreseen in the justification as presented. They include but are not limited to:

- Fewer smokers switching to vaping
- More vapers relapsing to smoking
- Teenagers smoking instead of vaping
- More teenagers switching to vaping cannabinoids such as THC
- Cross-border sales of flavoured e-liquids
- More home mixing of flavoured liquids (with additional risks)
- Black market trade in flavoured liquids and flavoured e-cigarettes
- Workarounds like selling flavours separately or use of food flavours
- Loss of legitimate retail and online businesses replaced by criminal networks or exporters from outside the Netherlands or European Union.

- 8. Fails to show benefits for adolescents or address concerns it may cause harm to young people.** The justification fails to articulate the benefit for youth. It does not show that:
- Flavours play an important causal role in adolescent vaping
 - A ban on flavours would reduce adolescent vaping, rather than just stimulate workarounds
 - If reductions in adolescent vaping were achieved as intended, this would translate to a benefit to health and not trigger an uptick in other risk behaviours.
- 9. Ignores the harmful effects of a vaping flavour ban on adults.** Where vaping displaces smoking – both in adults and adolescents – there are health, welfare, and economic gains for the users and for society. These benefits have been largely ignored in the reasoning presented to support the ban. The government's own target is to be smoke-free by 2040 – the substitution of smoke-free alternatives in place of cigarettes will be critical in meeting that target.
- 10. Creates regulatory protection for the cigarette trade.** The case does not recognise that vaping is an alternative to smoking and a pathway for smoking cessation and that flavours are an important part of the experience for adults. In obstructing this pathway and making it practically harder and less attractive for smokers to switch or risking that vapers will relapse to smoking, the proposals amount to a regulatory defence of the cigarette trade. While this is unlikely to be the government's intention, it may well be the perverse effect of this proposed intervention. It is quite possible that the e-cigarette flavour ban will protect the cigarette trade and increase smoking, resulting in more disease and death. Nothing in the memorandum provides an adequate counter to these concerns. The government should adopt "risk-proportionate regulation", which encourages producers and consumers to migrate from high-risk to low-risk products — rather than unjustified regulation that will inhibit switching away from smoking.
- 11. Violates important regulatory principles, including those underpinning the European Union internal market.** The proposed measure is disproportionate, discriminatory, anti-competitive, and counter to the aims of the European Union internal market. A key competitive advantage of e-cigarettes over cigarettes is the availability of diverse flavours (other than tobacco flavour)⁽¹¹¹⁾. The availability is important because most adult users prefer these non-tobacco flavours^(98,221). The proposed measure is indiscriminate in banning all but one flavour and does not adequately show that all non-tobacco flavours or descriptors have appeal to youth.

12. Proposes an illiberal policy and fails to recognise a major global public health opportunity. Though it is a political judgment, the measure appears to be excessively illiberal in its intrusion in adults' rights to protect their own health, on their own initiative, and at their own expense – or simply to use nicotine in a much safer way, if they choose to. It sets a precedent for governments to use potential risks to youth to curtail reasonable adult free choices. The aim should be to use targeted measures to control youth risks, not general measures that target all users. The policy overreacts to relatively minor and manageable risks but denies or ignores a significant opportunity to help millions of smokers radically reduce their health risks. In its role as Chair of the WHO Framework Convention on Tobacco Control Conference of the Parties in 2021, the Netherlands should be leading a positive approach to tobacco harm reduction.

b. Health Canada (September 2021)

During September 2021, Health Canada also conducted a public consultation on the use of flavours in nicotine vaping products (ENDS)⁽²⁴⁷⁾. Below I have attached the submission by 4 public health experts as well as my own:

- (i) *Submission by Prof David Abrams, Raymond Niaura, David Swenor and Clive Bates: The case against banning flavours in Canada* ([Link](#))⁽²⁴⁸⁾

Summary

Health Canada's case for banning vaping flavours as described in the memorandum supporting the measure is wholly inadequate, and the measure should not proceed on this basis. A realistic evidence-based appraisal would show the measure to be both economically damaging and detrimental to public health. The critical weaknesses are set out in the six sections of this submission and summarised here:

- **Section 1.** The objective, *reducing youth vaping*, is ill-conceived. This would be a poor objective if it meant more smoking among young people, fewer adults switching to vaping, and more adults relapsing to smoking. All of these consequences are likely. The objective should be to reduce *harms*, not just modify one behaviour in a mix of tobacco and substance use behaviours.
- **Section 2.** The analysis ignores likely unintended consequences arising from a flavour ban, making the naive assumption that young people will respond to a flavour ban by doing nothing or something virtuous instead of vaping.

However, there is a wide range of possible harmful responses to a vape flavour ban, including smoking, other substance use, black market access and participation, home mixing, and various workarounds. These do not feature in the justification.

- [Section 3](#). The justification is based on a flawed understanding of the causes of teenage vaping and a greatly overstated role for flavours. Vaping, like smoking, is not primarily driven by product features like flavours. It arises from deeper causes genetics, mental health, parental influence, community environment etc. Leaving the deeper causes intact while modifying a superficial influence will just cause a shuffling in the mix of risk behaviours.
- [Section 4](#). The analysis understates or ignores the significant role that vaping and vaping flavours play in smoking cessation and displacement backed by evidence from multiple sources: clinical trials, observational studies, population data trends, market data and stock analyst insights, economic analyses and natural experiments, and thousands of user testimonies.
- [Section 5](#). Health Canada has not developed the chain of reasoning necessary to show a flavours ban would have an overall positive effect. It would need to go show the flavour ban would positively affect vaping use and uptake, not lead to more adolescent smoking, and would not have adverse effects on adult tobacco use behaviours. This failure is most overt in the cost-benefit analysis.
- [Section 6](#). The cost-benefit analysis on which the justification rests is fundamentally flawed. It is built on a false gateway assumption that teenage vaping leads to adult smoking and that the impact of a vaping flavour ban will reduce future smoking. There is no basis for claiming a gateway effect, and an alternative “common liability” explanation for the data is far more credible. Over 93 percent of the public health benefits shown in the cost-benefit analysis break-even case relate to avoided *smoking-related impacts*. Yet, the evidence suggests vaping is a substitute for smoking and is more likely to divert adolescents from smoking. Under closer examination, the case falls apart.



(ii) *Submission by Dr. Konstantinos Farsalinos (2 September 2021)*

Comments on the Health Canada Order Amending Schedules 2 and 3 to the Tobacco and Vaping Products Act (Flavours) and the proposed Standards for Vaping Products' Sensory Attributes Regulations.

**Honourable Madam / Sir, Manager of the
Vaping Products Division, Health Canada,**

As a scientist with an established work and publication record in the field of smoking and tobacco harm reduction, I am sending this letter in order to kindly present my views in relation to the Canadian Federal Government's draft Order to amend the Tobacco and Vaping Products Act.

I welcome the initiative to strengthen the regulatory framework in order to further reduce smoking prevalence in Canada, However, I urge the government to carefully consider the totality of evidence concerning e-cigarettes and to examine the possibility that they are an important part of the solution in the smoking problem. E-cigarettes currently appear to be the method of choice for smokers to quit and can play a significant role in preventing tobacco-related disease and premature death. This product category can literally save lives.

Therefore, it has been most concerning that the Tobacco and Vaping Products Act would restrict flavours in vaping products to only tobacco, mint, and menthol. It is important to acknowledge the important role that flavoured e-cigarette products are playing in reducing the harms caused by smoking. From a health perspective, the major distinction between nicotine products is based on the presence or absence of combustion. It is well known that it is smoke, not nicotine, which causes almost all of the smoking related diseases. Non-combustible products have a clear role to play in reducing smoking prevalence to meet the ambitious objectives set by the government.

On the subject of smoking cessation, there is increasing evidence from Randomised Controlled Trials (RCTs), designed specifically to explore effects on tobacco smoking, that vaping products (e-cigarettes) can help smokers quit. A Cochrane review published in 2016⁽¹²⁷⁾ concluded that smokers using an e-cigarette were more likely to quit compared to those using a placebo at 6 months. More recently, a RCT of e-cigarettes versus Nicotine Replacement Therapy (NRT) alongside behavioural support in England, reported an almost two-fold increase in 12 month quit rates with e-cigarettes⁽³⁾.

A survey conducted in 4618 participants showed that adult e-cigarette users (most of whom were former smokers) were using a variety of different, non-tobacco, flavours⁽⁹⁶⁾. In another study of > 60.000 adult vapers (again most of them were former smokers), the vast majority eventually transitioned to fruit, dessert or candy flavours that do not resemble and did not remind them of



the taste and experience of tobacco cigarettes⁽⁹⁸⁾. This clearly indicates that flavours are marketed in order to satisfy adult vapers' demand. They appear to contribute to both perceived pleasure and the effort to reduce cigarette consumption or quit smoking. Therefore, implementing regulatory restrictions to flavours could cause harm to current adult vapers. Eliminating flavours in e-cigarettes or applying other restrictions that reduce the attractiveness of e-cigarettes for smokers will defeat their public health purpose, aims and gains already made in smoking cessation.

Moreover, policies restricting access to flavours are unlikely to achieve their stated goals and are likely to have unintended consequences. A "flavour ban" may increase teen harms. There is broad agreement that no one wants under-age persons to vape. Concerns have been raised from data in the US that teen e-cigarette use has increased over the years. However, most use is infrequent, experimental and largely confined to teens with a smoking history⁽²⁴⁹⁾. Furthermore, the increase in experimental e-cigarette use has coincided with the largest reduction in teen smoking rates, which are now at historically low levels. Flavours are only the third most prevalent reason for e-cigarette use among US teens. But even if a flavour ban does marginally reduce the illegal behaviour, I need to ask – how many adult lives are we willing to put at risk, and how many smokers will miss the opportunity to reduce their health risks in order to achieve that goal? A recent study found that non-tobacco flavours was no more associated with youth smoking initiation than using tobacco flavours but was associated with increased adult smoking cessation⁽⁸⁾. Additionally, a flavour ban would not prevent teens who want to engage into such a behaviour from seeking other legal sources of flavours, such as products used by the food industry. This will in fact create an uncontrolled market in terms of product quality and regulation. Other studies have reported that restrictions in e-cigarette availability might even promote smoking^(250,251). Ultimately, there is insufficient evidence that a flavour ban will reduce underage vaping, but there is evidence that such bans might not achieve that goal and could harm adult smokers. The European Union has an established regulatory framework on e-cigarettes which includes a ban on the sales to youth. The best approach that would prevent unintended consequences is undoubtedly the strong implementation and enforcement of the current regulation concerning the sales ban to youth.

In addition, as is the case across the globe, there are many smokers in Canada who are unable or unwilling to quit, not least of all the poorest and most disadvantaged in society who find smoking cessation the most difficult. This large group, including those suffering from mental illness, would benefit from switching to smoke-free products. In this regard it is critical that adult smokers can be informed about these innovative products and receive balanced, reliable and accurate information about their relative risk.



However subjecting e-cigarettes and other combustion-free products to the same restrictions as for combustible cigarettes can have unintended consequences. It is practically misinforming smokers about the relative risks of e-cigarettes compared to tobacco cigarettes, discourages them from making the switch, and will eventually favour the tobacco industry. How is this possible? As articulated by the Royal College of Physicians⁽²⁾: "If [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking." (Section 12.10 page 187).

A horizontal implementation of similar restrictions on e-cigarettes as for tobacco cigarettes also defies the risk proportionality principle, a fundamental approach in preparing public health regulatory frameworks, and is contradictory to the overwhelming evidence on the lower harm potential of e-cigarettes compared to smoking. Such a proposal is likely to result in net public health harm and will harm the smoking population.

Finally, may I reiterate that whilst I welcome tighter restrictions on cigarette smoking, banning flavoured e-cigarettes will discourage smokers from switching, which leads to the unintended consequence of continuous and prolonged smoking. Instead, the authorities should focus on successfully enforcing the current regulatory framework which includes a ban on the sales of these products to youth.

I respectfully ask the government to carefully assess the role of flavours in non-combustible products such as e-cigarettes, specifically in reducing smoking prevalence and preventing tobacco-related disease and death. I would welcome the opportunity to contribute to any consultation, should you decide to organize such type of event.

Note *In my email, I also attach the draft of an online cross-sectional survey of almost 70,000 US adult e-cigarette users, examining patterns of e-cigarette flavour use⁽⁹⁸⁾. The study was submitted to the US FDA advance notice of proposed rulemaking (ANPRM) which was issued in 2018 in order to obtain information related to the role that flavours play in the population's use of tobacco products.*

Yours sincerely

Konstantinos Farsalinos, MD, MPH

*External Research Associate University of Patras,
Greece School of Public Health, University of West
Attica, Greece Highly Cited Researcher 2019*

7. CONSUMER DIMENSION: WHAT DO CONSUMERS SAY ABOUT FLAVOURS?

Consumers have not been given a “seat at the table” in the debate on the role of tobacco harm reduction in tobacco control. This dimension must be rectified.

In this section, the compelling testimony of users / consumers of flavoured ENDS are included. These testimonies should be used in building a case from a consumer point of view, drawing on multiple strands of evidence (forensic, phone records, identification, financial records, witnesses, etc.).

Below I have provided links to literally thousands of consumer testimonials, of how (flavoured) nicotine vaping products have improved their quality of life, and in many cases – saved them from a premature death. I count as one of those consumers!

To demonstrate the general views of consumers, I have selected a number of consumer and other health advocate's views on flavours, in various parts of the world.

a. **Netherlands Consultation on E-Cigarettes (Overheid.nl)**

Consumers and Consumer Advocates

A public consultation on e-cigarette use and the introduction of a flavour ban in the Netherlands was published in December 2020⁽²⁵²⁾. The consultation was organised by the Dutch Ministry of Health, Welfare and Sport and conducted by the Trimbos Institute. Several tier 1 and tier 2 consumer advocates and public health influencers sent submissions detailing their opinions on the proposal. Michael Landl, director of the World Vapers' Alliance, argued against the implementation of a flavour ban. He stated that “[f]lavoured vaping is a smoking cessation option that significantly reduces harm to the user while increasing the likelihood of success.” His full submission can be read [here](#)⁽²⁵³⁾.

Lorenzo Montanari, executive director of the Property Rights Alliance and VP of international affairs for Americans for Tax Reform, said “[b]anning flavours may lead to continuous and prolonged smoking, as it would damage a harm reduction tool... [b]anning vape flavours practically misinforms smokers about the relative risks of e-cigarettes and limits the usefulness of vaping as a tobacco harm reduction tool.” His full submission can be read [here](#)⁽²⁵⁴⁾.

A third tier 1 contributor was Maria Chaplia, research manager at the Consumer Choice Center. She said “[a] nationally representative longitudinal study of over 17,000



Americans, over a five-year period, showed that adults who used flavoured vaping products were more likely to quit smoking cigarettes when compared to vapers who consumed tobacco flavoured vaping products. When comparing the two groups, those who use flavours and those who use tobacco flavours, vapers that used flavours were 2.3 times more likely to quit smoking than those vaping tobacco flavoured products.” She added that adults find vaping more satisfying than smoking when there are flavours. Her full submission can be read [here](#)⁽²⁵⁵⁾.

Public Health Advocates

Dustin Dahlmann, chairman of the Independent European Vape Alliance, said “[f]lavours other than tobacco are a significant factor of success for smokers in their attempts to quit smoking.” He particularly criticised the misconception that flavours lead to youth uptake. “E-liquids with flavours other than tobacco are not a gateway to youth uptake of smoking. No evidence substantiates the association between vaping flavours and subsequent smoking initiation,” he wrote. His full submission can be read [here](#)⁽²⁵⁶⁾.

Several public health advocates, including Clive Bates, David Abrams, Konstantinos Farsalinos, Lynne Dawkins, Jean-Francois Etter, Peter Hajek, Ron Borland, Jacques Le Houezec, Lion Shahab, Karl Erik Lund, Raymond Niaura, David Sweanor and Umberto Tirelli sent in a joint submission. In it, they argued that a flavour ban pushes a “war on drugs” against nicotine, relies on false and misleading claims about e-cigarettes, ignores harmful effects of flavour bans on adults and makes claims about youth vaping and the “gateway” effects. Their full submission can be read [here](#)⁽²⁵⁷⁾.

In his submission, Christopher Snowdon, head of lifestyle economics at the Institute of Economic Affairs, said “[u]nflavoured e-cigarette fluid is rarely consumed by vapers. ‘Tobacco’ flavour only vaguely resembles the taste of smoked tobacco and is an artificial flavour like any other. Some vapers like it, others do not. To encourage smokers to switch to vaping, it is important to have a wide range of flavours available.” He added that few vapers cite flavours as a reason to start vaping, explaining that smokers turn to vaping and then continue to vape because of the wide variety of flavours available. His full submission can be read [here](#)⁽²⁵⁸⁾.

Center of Excellence for the Acceleration of Harm Reduction (CoEHAR) said “[a] flavour ban cannot substantially decrease youth use of e-cigarettes because curiosity is the primary motivation for youth to experiment with e-cigarettes.” Polosa went on to write that “[a] flavour ban will certainly reduce the number of adults who will successfully quit smoking by substituting e-cigarettes for cigarettes. A US study calculated that adults under 55 years old who used non-tobacco flavoured e-cigarettes were 228% more successful at quitting smoking than adults who used tobacco flavoured e-cigarettes. Another study found that adults who quit smoking with flavoured e-cigarettes were 283% more successful at being quit for one year or more than adults who used tobacco-flavoured e-cigarettes.” His full submission can be read [here](#)⁽²⁵⁹⁾.

b. European Union SCHEER Report on electronic cigarettes

Consumer Advocates

In 2020, the European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published a report that argued against the health benefits of e-cigarettes⁽²²⁰⁾. In this report, they called for public consultation submissions. Several tier 1 and tier 2 consumer advocates and public health influencers submitted their opinions. The World Vapers' Alliance (WVA) published a report that criticised several points that SCHEER made⁽²⁶⁰⁾. Regarding flavours, they said “[f]lavourised vapes are crucial tools for adult smokers to quit smoking. They have achieved what legislation and taxation could not. By not reminding vapers of the taste of tobacco, flavours are more likely to keep people off traditional cigarettes.” Their full submission can be read [here](#)⁽²⁶⁰⁾.

The European Tobacco Harm Reduction Advocates (ETHRA)'s submission argued that flavours are a necessary component of smoking cessation. “Attractive flavours are critical factors in the effectiveness of e-cigarettes for smoking cessation, also why Nicotine Replacement Therapy products come in a range of fruity and mint/menthol flavours.” Their full submission can be read [here](#)⁽²⁶¹⁾.

The Consumer Choice Center's (CCC) submission to the public consultation said flavours play a key role in helping smokers quit and the legislation must reflect that⁽²⁴²⁾. “Survey results from the [longitudinal survey study from Yale School of Public Health](#)⁽⁸⁾ found that ‘relative to vaping tobacco flavours, vaping non-tobacco flavoured e-cigarettes was not associated with increased youth smoking initiation,’ they wrote. “But was associated with an increase in the odds of adult smoking cessation.” Their full submission can be read [here](#)⁽²⁶²⁾.

Public Health Experts

Clive Bates' submission to the consultation criticised SCHEER's suggestion that the attractiveness of flavours is bad. He argued that flavours being attractive is a good thing because it draws smokers away from traditional cigarettes and towards vape products. He said “[i]n a situation where 26% of European Union adults are smoking and approximately 700,000 dying as a result annually, the availability of an attractive low-risk alternative provides options for smokers to switch and greatly reduce their personal risk – on their own initiative and at their own expense *because they find the idea attractive.*” His full submission can be read [here](#)⁽²⁶³⁾.

c. Health Canada Consultation on ENDS / Nicotine Vaping Products

Consultation on proposed vaping products' flavour regulations and order was an online consultation, which closed on September 2nd⁽²⁶⁴⁾.

Public Health Advocates

As mentioned before, Clive Bates published a response from himself, Professor David Abrams, Professor Raymond Niaura and Professor David Swenor. In the 17-page document's six sections, they argued that the objective was ill-conceived, that the analysis ignored the unintended consequences, that the justification for such a move was based on a flawed understanding of teen vaping, that the analysis understated or ignored the role vaping and vaping flavours play in smoking cessation, that Health Canada had not shown that such a move would be of overall benefit and that the cost-benefit analysis is flawed. "Health Canada's case for banning vaping flavours as described in the memorandum supporting the measure is wholly inadequate, and the measure should not proceed on this basis. A realistic evidence-based appraisal would show the measure to be both economically damaging and detrimental to public health," they wrote. Their response can be read [here](#)⁽²⁴⁸⁾.



8. UNINTENDED CONSEQUENCES OF FLAVOUR BANS (IN ENDS / NICOTINE VAPING PRODUCTS)

If flavour bans were to be considered by national regulators, to help stop youth initiation of vaping, they need to be aware of the possible unintended consequences of such bans. Given the known harms of smoking, it is unclear why a government or public health authorities would wish to intervene to regulate e-cigarettes in a way that degrades the competitive advantage of e-cigarettes relative to cigarettes and provides anti-competitive support for the cigarette trade. The Royal College of Physicians (London) explained this issue⁽²⁾:

Royal College of Physicians. Nicotine without smoke: tobacco harm reduction. London: RCP; 2016. [[link](#)] (Section 12.10 page Page 3 of 17).

However, if [a risk-averse, precautionary] approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking. Getting this balance right is difficult.

a. **Potential unintended consequences of flavour bans (in ENDS / nicotine vaping products)**

B (i) Clive Bates, from [Counterfactual Consulting](#), explains how such measures could perpetuate smoking and related harms include⁽²⁴⁸⁾:

- *Reduced adult smoking cessation.* Adult smokers are at far greater and more immediate risk of serious disease than any teenage vaper. If Canada wishes to address the Sustainable Development Goal objective to reduce non-communicable disease burdens by one-third by 2030, it will need a relentless focus on adult smoking cessation. The harms avoided by a middle-aged adult quitting smoking are two orders of magnitude greater than the harm avoided by preventing vaping in an adolescent who would not have otherwise used nicotine.
- *Harm to adolescents arising from adult smoking.* The smoking behaviour of parents or other significant adults causes harm to young people through role-model effects that transmit smoking prevalence between generations, welfare and economic impacts on the family, caring burdens and grief associated with death or incapacitation, and direct exposure to tobacco smoke.

The most disadvantaged young people (those most likely to smoke) benefit from the availability of attractive vaping products as an option for quitting smoking later in life.

- *Reduced adolescent smoking cessation.* If vaping enters into the mix of young adult tobacco-use behaviour, it might be beneficial, if they would otherwise be smoking.
- *Reduced diversion of young people from smoking at initiation or soon after.* Population-level evidence shows that vaping functions as a diversion from smoking for young people in the United States. This is consistent with observed US adolescent population trends. Policies that reduce adolescent vaping will likely reduce the impact of a diversionary effect and so cause a relative increase in smoking and harm.
- *Increased black market activity.* A black market of unregulated versions of prohibited products will inevitably form, the question is how large and how quickly it will grow. Even if smaller than the current legitimate market, it will be more harmful, increasing exposure of young people to a range of illegal substances and criminal networks as well as unregulated vaping products. A ban on vaping flavours could, via contact with criminal networks, become a gateway to cannabis, opioids and criminal engagement. Entrepreneurial young people will also be empowered to source and sell prohibited products for which there is continuing demand, thus entering criminal supply chains as economic actors.
- *Increase in informal DIY home mixing of flavours.* Bans on flavours will increase risks arising from poor hygiene and experimentation with risky ingredients, including a wholesale trade in high strength nicotine liquids that would not be permitted or needed in the normal consumer environment.
- *Workarounds.* Sales of flavour agents will continue as additives to food or drink or for purposes like aromatherapy. To the extent these are successful and widespread, they may mitigate some of the harms listed above while further illustrating the lack of feasibility for these regulations.

b. Landmark Studies: Impact of flavour bans on usage and smoking cessation

Landmark study by Abigail Friedman:

In 2018, San Francisco voters overwhelmingly approved a ballot measure to ban flavoured tobacco products⁽²⁶⁵⁾. Whilst this was initially celebrated by many public health advocates, it was later revealed in a study to have had unintentionally deleterious consequences: an increase in youth smoking since the flavour ban was

implemented (Table 8). Published in 2021, Associate Professor Abigail Friedman's study provided a scientific basis for the "unintended consequences" of flavour bans: "San Francisco's flavour ban was associated with more than doubled odds of recent smoking among underage high school students relative to concurrent changes in other districts (adjusted odds ratio, 2.24 [95% CI, 1.42-3.53]; P = .001)"⁽⁹⁾

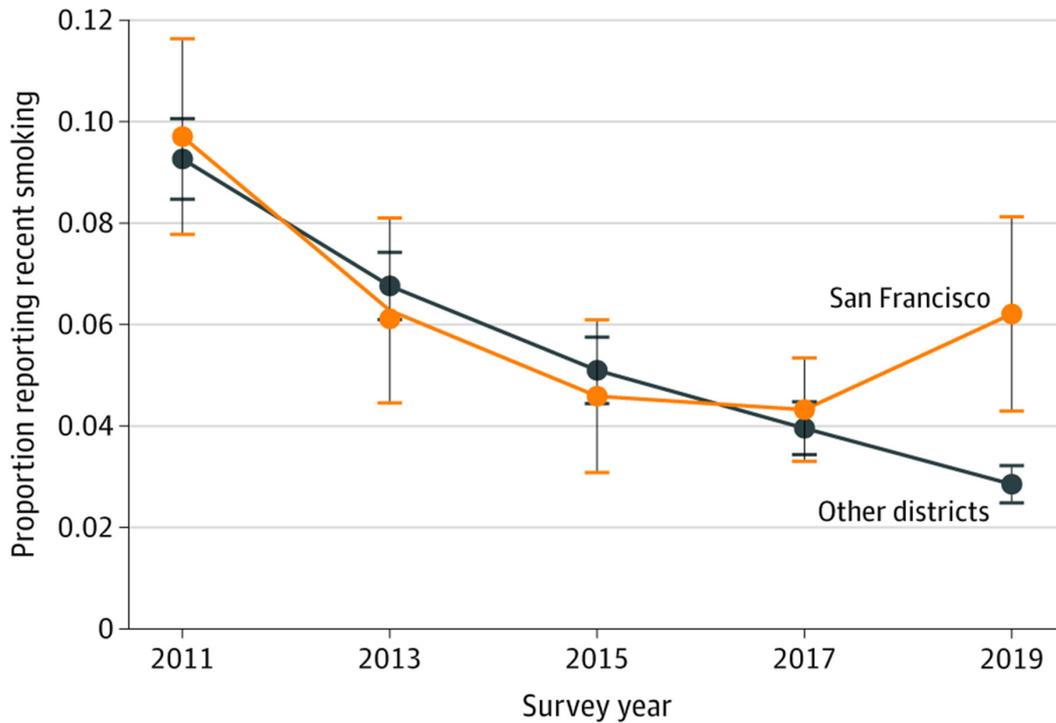


Table 8: Past-30-Day Smoking Trends Among High School Students Younger Than 18 Years⁽⁹⁾.

- **Lost opportunity to help more smokers quit cigarettes**

Adults who vape non-tobacco flavours are more than two times likely to quit smoking than those who vape tobacco flavours: "Vaping nontobacco flavours was no more associated with youth smoking initiation than vaping tobacco-flavours (AOR in youth, 0.66; 95% CI, 0.16-2.76; P = .56) but was associated with increased adult smoking cessation (AOR in adults, 2.28; 95% CI, 1.04-5.01; P = .04)."⁽⁸⁾

- **Illicit trade: People resort to the Black Market to acquire flavours**

In the Consumer Choice Centre's 'Why Vape Flavours Matter' report, the authors stated: "As prohibition always does, a ban on flavoured vaping products creates an incentive for some to continue to offer those products illegally. While this might sound far-fetched to some, investigations in the states of New York, New Jersey, and Massachusetts have already shown that a booming black market has emerged in response to flavour bans. Massachusetts authorities have publicly stated that the state's flavour ban will inflate the size of their illicit tobacco market, which is more than \$10 billion."⁽²⁴²⁾

The report drew on evidence of this phenomenon from New York State: “One e-liquid manufacturer in New York State, who told Filter he acquired 10 gallons of liquid nicotine before the state ban became a reality, just leased a new property to produce and sell his homemade flavours to his hundreds of established customers. “I’m set for a few years,” he claimed.”⁽²⁶⁶⁾

And from Sydney, Australia: “One criticism of these proposed restrictions is they could produce unintended consequences, such as the spawning of black markets or migration to tobacco. Rachel, a 24-year-old from Sydney, told The Feed that she’d rather just buy tobacco, despite transitioning to an e-cigarette eight-months-ago over health concerns, than have to hassle with sourcing liquid nicotine.”⁽²⁶⁷⁾

- **People cross borders to buy flavours in legal jurisdictions**

A further caution on flavour bans from the Consumer Choice Centre’s report: “In many instances, consumers will respond to a flavour ban by purchasing their preferred flavoured products in jurisdictions where they are legal, across state or national borders, and bringing them home. This is especially true for populations located nearby alternative jurisdictions and with open travel (US states, the EU). For example, the U.S state of Massachusetts recently banned all tobacco and vaping flavoured products. As a result of the ban, consumers en masse purchased those products in the nearby states of New Hampshire and Rhode Island (which do not have similar bans). The size of that consumer shift was considerable. New Hampshire’s flavoured product sales jumped as high as 150%, generating an additional \$9 million more in tax revenue when compared to the previous year (before the Massachusetts ban). Rhode Island’s flavoured product sales jumped as high as 157% generating \$5.7 million in additional tax revenue. It is reasonable to assume that consumers in similarly situated jurisdictions will respond by simply purchasing those prohibited products in legal jurisdictions.”⁽²⁴²⁾

B (ii) Landmark study by Shannon Gravely et al

The International Tobacco Control Project Four Country Smoking and Vaping (ITC 4CV) Survey⁽²⁶⁸⁾ is a cohort study of parallel online surveys conducted in Canada, US, England, and Australia. The lead author, Shannon Gravely reported that:

- The majority of vapers who use non-tobacco flavored nicotine vaping products (NVPs) oppose flavor restrictions.
- Predicted behavioral responses to a hypothetical NVP flavor ban were mixed, and largely varied by smoking and vaping status, and by the level of support of a flavor restriction policy.
- Most vapers said that if non-tobacco flavors were banned they would either continue vaping an available flavor or find a way to get banned flavors.

9. CONCERNS THAT NEED TO BE ADDRESSED

a. ENDS / Electronic cigarette use by never smokers and youth

Scientists and regulators are particularly sensitive about youth. Smoking, or use of any substance, is definitely undesirable for this age group. Despite the ban on the sales of tobacco cigarettes that have been implemented throughout the world, youth still initiate smoking. Smoking prevention should be the priority for this age group. There is reasonable concern about the use of electronic cigarettes by never smokers. Studies examining the smoking status of adult electronic cigarette users show that they are predominantly current or former smokers. In the latest analysis in the UK, 2.9% of current electronic cigarettes were never smokers, representing 0.3% of the never smoking population⁽¹³⁵⁾. In the European Union, only 0.2% of never smokers were using electronic cigarettes in 2014, with daily nicotine use being rare (0.04%)^(39,136). Similar patterns of use has been observed in the adult US population and in other countries^(56,269-276). Therefore, current evidence suggests that the pattern of electronic cigarette use by adults is favourable for public health since the products are not appealing to never smokers. Obviously, continuous monitoring is needed in order to rapidly identify any changes in the use patterns.

Another issue that has generated a lot of controversy is the use of electronic cigarettes by adolescents. In 2016, the US Surgeon General declared that electronic cigarettes are a major public health concern in a report presenting a large increase in ever use among adolescents from 2011 to 2016⁽²⁷⁷⁾. Findings from two large surveys of US youth were presented, the National Youth Tobacco Survey (NYTS) and the Monitoring the Future Study (MTF)⁽²⁷⁸⁻²⁸¹⁾. While ever and current (past 30-days) use has increased over time, the report failed to discuss in detail the frequency of use and the past and current smoking history of electronic cigarette users. Differentiating experimentation from regular use is important both for health risk and for the likelihood to become long-term users. Nicotine use is also important in determining the dependence potential. The 2014 NYTS found most electronic cigarette users had also used other tobacco products, while frequent use by never smokers was rare⁽²⁸²⁾. Similar findings were reported in an analysis of the 2014 MTF survey⁽²⁸³⁾. Additionally, most adolescent users were not using nicotine-containing electronic cigarettes⁽²⁸³⁾. Data from the 2015 NYTS revealed that, while 11.1% of US youth reported having used an electronic cigarette at least once in the past 30 days (i.e. current users) only 1.7% has used an electronic cigarette on at least 20 of the past 30 days (i.e. frequent users)⁽²⁸⁴⁾. More importantly, only 0.3% of never-smoking youth reported using electronic cigarettes for at least 20 of the past 30 days, with only 0.2% using them daily. In 2018 and 2019, 0.44% and



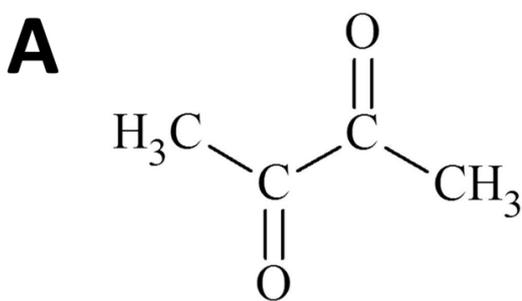
1.38% of never-smoking youth reported using electronic cigarettes frequently^(132,249). Smoking youth were 17 times more likely to be current electronic cigarette users compared with never-smoking youth^(132,249). Another issue that can create confusion relevant to the use of electronic cigarettes, as reported in US population surveys, is the use of these devices to inhale marijuana. This has been a recent trend in the US, and a recent study showed that up to almost 70% of electronic cigarette users have ever used marijuana in an electronic cigarette⁽²⁴⁹⁾. Unfortunately the survey only examined ever marijuana use; thus, it is not possible to determine what proportion of participants may be using electronic cigarettes predominantly or exclusively for marijuana use. Results from the Monitoring the Future Study, another school-based national survey in the US, though, indicate that there is substantial overlap among use of marijuana, cigarettes and electronic cigarettes⁽²⁸⁵⁾. A recent study concluded that the data from 2017, 2018 and 2019 NYTS reported that dependence to electronic cigarettes remained rare in youth who had never used any other tobacco product. Similar findings of considerable experimentation among youth but little regular use has been observed in UK adolescents^(286,287). An analysis of 5 cross-sectional surveys in the UK reported that most electronic cigarette experimentation did not translate into regular use, while levels of regular use in young people who have never smoked were low⁽²⁸⁷⁾.

Another crucial research question is whether electronic cigarettes may act as a gateway to or a gateway from smoking in never smoking adolescents. There is evidence that electronic cigarette use at baseline is associated with subsequent smoking⁽²⁸⁸⁻²⁹²⁾. A meta-analysis estimated electronic cigarette use may increase by 3 to 4-fold the odds of using tobacco cigarettes⁽²⁹³⁾. While the authors concluded that there is a causal link, mainly because temporality was established, a reverse temporal association has also been observed. Leventhal et al. reported that baseline ever use of a combustible tobacco product was positively associated with electronic cigarette use at both 6- and 12-months follow-up⁽²⁸⁸⁾. An alternative explanation to the gateway hypothesis is that common factors could lead to both electronic cigarette and tobacco cigarette use. Such factors include sensation seeking, impulsivity and tendency to engage into risky and controversial behaviours, which could predispose youth to trying both electronic cigarettes and tobacco cigarettes⁽²⁹⁴⁾. This refers to the common liability theory^(295,296), which could explain the tendency of young people to experiment with smoking and electronic cigarettes. Further support for the common liability theory comes from data consistently showing a marked decline in smoking rates from 2011 to 2020, despite the growing electronic cigarette use experimentation⁽²⁹⁷⁾. Continuous monitoring of smoking and electronic cigarette use rates by youth is needed in order to determine whether they act as gateway to smoking or as a distraction from smoking.

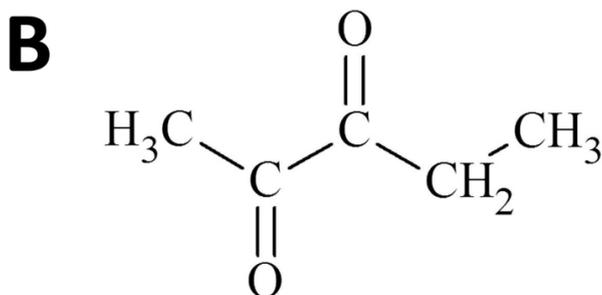
b. SAFETY aspects of flavours

An example of compounds that are safe for ingestion but raise safety concerns when inhaled are diacetyl and acetyl propionyl. Diacetyl (also called 2,3-butanedione, CAS 431-03-8, Table 9) is a diketone. It is a volatile liquid and has a boiling point of 88°C⁽²⁹⁸⁾. It has a low odour threshold concentration, approximately 0.05 to 4 µg/L in water^(298,299) and 0.01 to 0.02 ppb in air⁽³⁰⁰⁾. It provides a buttery and creamy flavour. It is naturally found in foods but it is also used as a synthetic flavouring agent in butter, cocoa, caramel, dairy products, coffee and alcoholic beverages⁽³⁰¹⁾, but it is also produced endogenously⁽³⁰²⁾. There are many ways of producing diacetyl synthetically^(298,302). It is also a by-product of fermentation. In mammalian cells, diacetyl is metabolized to acetoin by diacetyl reductase. This enzyme is present in rat liver, kidney and respiratory epithelium^(298,303-306). Additional metabolic pathways exist in the lungs^(307,308).

Acetyl propionyl (also called 2,3-pentanedione, CAS No. 600-14-6, Table 9), is also an α -diketone. It is a yellowish liquid with a boiling point of 108°C⁽²⁹⁸⁾. Its odour threshold concentration is 0.01-0.02 ppb in air and 30 µg/L in water. It provides a buttery flavour. It also occurs naturally meat, seafood, fruits and alcoholic beverages⁽¹⁰⁹⁾. Synthetically, it can be produced by different methods⁽²⁹⁸⁾. In mammalian cells, it is metabolized diacetyl reductase⁽³⁰³⁾.



Diacetyl (2,3-butanedione)



Acetyl propionyl (2,3-pentanedione)

Table 9: Chemical structures of diacetyl (A) and acetyl propionyl (B).

Both compounds are considered safe for ingestion but there are concerns about their local effects on the lungs when inhaled. It has been suggested that diacetyl inhalation may be associated with the development of bronchiolitis obliterans, a condition characterized by irreversible alterations in bronchioles that lead to concentric narrowing, or even complete obliteration, of the airway lumen. Bronchiolitis obliterans is a clinical condition associated with chronic allograft dysfunction after lung transplantation⁽³⁰⁹⁾. It is diagnosed by lung biopsy, but diagnosis may be missed because of the patchy distribution of lesions^(310–312). It has also been observed after lung infections or exposure to chemicals^(277,313,314).

A clinical condition suggestive of bronchiolitis obliterans was observed in workers of a manufacturing plant producing diacetyl⁽³¹⁵⁾. In May 2000, some workers at a plant producing microwave popcorn were diagnosed with bronchiolitis obliterans⁽³¹⁶⁾. An association between diacetyl inhalation in the occupational setting and lung disease was first suggested in 2002⁽³¹²⁾. Other cases of bronchiolitis obliterans were identified in another facility⁽³¹⁷⁾. Several other studies have examined the link between exposure to buttery flavours and development of respiratory dysfunction, especially in the microwave popcorn industry^(318–324). Due to this, the condition was named “popcorn worker’s lung”. Most cases were diagnosed based on clinical criteria instead of lung biopsy. However, the studies also found higher prevalence of respiratory dysfunction, without the development of bronchiolitis obliterans, in workers who have been exposed to buttery flavours.

Experimental studies in animals examined whether diacetyl exposure leads to lung damage. Diacetyl inhalation caused damage to the nasal and respiratory epithelium in rats, as well as necrotizing rhinitis, and inflammation⁽³²⁵⁾. Similar findings were reported in mice⁽³²⁶⁾. The intratracheal instillation of large doses of diacetyl resulted in the development of bronchiolitis obliterans⁽³²⁷⁾. In vivo animal experiments of exposure to acetyl propionyl were also performed since it was subsequently used by the food flavouring industry instead of diacetyl⁽³²⁸⁾. Bronchial fibrosis, inflammation and increased airway reactivity was observed as a result exposure to the compound^(329–332). However, it is unclear how these effects can be translated to human effects.

The data led to the implementation of acceptable occupational exposure limits in order to protect workers (Table 10)⁽²⁹⁸⁾. NIOSH reported that the established limits would be associated with a 1 in 1000 excess prevalence of pulmonary dysfunction after 45 years of exposure. The European Commission has also published recommendations for occupational exposure to diacetyl, setting limits which were higher than those set by NIOSH⁽³³³⁾. In 2012, ACGIH adopted TLVs for diacetyl, including a 15-minute STEL of 0.02 ppm (70 µg/m³) and an 8-hour TWA of 0.01 ppm (35 µg/m³)⁽³³⁴⁾.

Table 10: Regulatory limits for occupational exposure to diacetyl and acetyl propionyl⁽²⁹⁸⁾.

Organization	Exposure time	Acetyl propionyl	Diacetyl
ACGIH	15 min STEL	not available	0.02 ppm (70 $\mu\text{g}/\text{m}^3$)
	8 h TWA	not available	0.01 ppm (35 $\mu\text{g}/\text{m}^3$)
European Commission	15 min STEL	not available	0.1 ppm (350 $\mu\text{g}/\text{m}^3$)
	8 h TWA	not available	0.02 ppm (70 $\mu\text{g}/\text{m}^3$)
OSHA	15 min STEL	not available	not available
	8 h TWA	not available	not available
NIOSH	15 min STEL	0.031 ppm (127 $\mu\text{g}/\text{m}^3$)	0.025 ppm (88 $\mu\text{g}/\text{m}^3$)
	8 h TWA	0.0093 ppm (38 $\mu\text{g}/\text{m}^3$)	0.005 ppm (18 $\mu\text{g}/\text{m}^3$)

Diacetyl and acetyl propionyl are also detected in tobacco cigarette smoke, with concentrations depending on the puffing regimes^(335–337). However, it was found that they are produced due to pyrolysis rather than emitted due to their use as flavouring additives. Thus, smoking exposure to diacetyl and acetyl propionyl cannot be avoided.

In 2014, a study analysed 159 liquids for the presence of diacetyl and acetyl propionyl^(108,338). Most of the samples were sweet-flavoured liquids, where diacetyl and acetyl propionyl are more likely to be used. Diacetyl or acetyl propionyl was found in the majority of the samples tested. However, cigarette smoke contains 100-fold and 10-fold higher levels of diacetyl and acetyl propionyl, respectively, compared to electronic cigarette aerosol. Both compounds were readily delivered to the aerosol of an electronic cigarette, without any indication of additional production due to liquid heating. Therefore, exposure can be avoided if these compounds are not used as flavouring additives. Another study measured the levels of these compounds in 51 electronic cigarette products⁽³³⁹⁾. Both compounds were found in most of the samples but at much lower levels compared to the previous study.

Some scientists doubt that there is a link between diacetyl inhalation and the development of bronchiolitis obliterans. This is based on the fact that smokers are exposed to high levels of diacetyl but do not develop bronchiolitis obliterans⁽³³⁷⁾. Some researchers examining lung function in workers exposed to diacetyl found that non-smokers had higher prevalence of airway obstruction compared to smoking workers^(312,322). These findings could even suggest that smoking may be protective⁽³¹²⁾. However, cigarette smoke contains several respiratory toxins which may act synergistically and cause different lung pathologies such as chronic obstructive lung disease which has a prevalence of 15.4% in smokers⁽³⁴⁰⁾. Moreover, the condition is often misdiagnosed since lung biopsy is the gold standard for identifying the condition,



while many smokers have histopathological features of respiratory bronchiolitis in post-mortem examinations⁽³⁴¹⁾.

In conclusion, there is some concern that diacetyl and acetyl propionyl inhalation through electronic cigarettes may be harmful, despite the fact that no such case has been identified until now among millions of users. While exposure through smoking is unavoidable, the source for these compounds in electronic cigarettes is through their use as flavoring additives, while further production from thermal decomposition is not expected to meaningfully increase exposure⁽³³⁸⁾. While further research is needed, a precautionary approach of removing these compounds from the list of ingredients suitable for electronic cigarette liquids may be warranted.

10. REGULATORY CONSIDERATIONS ON ENDS & FLAVOURS

For electronic cigarettes to be an effective harm reduction and tobacco cessation public health strategy, a robust and proportionate regulatory framework is a requirement. The best example of a comprehensive and fully implemented regulatory framework on electronic cigarettes exists in the European Union: The Tobacco Products Directive, promulgated in 2014, and adopted into national legislation of all member states in 2016⁽¹⁰⁹⁾. The Tobacco Products Directive integrates electronic cigarettes into the regulation for tobacco products, but under a separate section that does not classify them as tobacco products. This is appropriate because they do not contain any tobacco. While nicotine in electronic cigarettes is derived from the tobacco plant, as is nicotine in pharmaceutical nicotine replacement therapies, this cannot scientifically justify the classification as a tobacco product in the same way that biodiesel cannot be considered a vegetable product because it is derived from plants⁽⁴⁴⁾. For specific cases, the Tobacco Products Directive allows the regulation of electronic cigarettes as medicinal products, but in almost all cases they are marketed as consumer products. Electronic cigarettes are excluded from many of the restrictions on combustible tobacco products, including the prohibition of flavours and the placement of health warning messages and pictorials on the packaging. The regulation includes quality standards, nicotine concentration and volume limits in electronic cigarette liquids and prefilled cartridges, marketing restrictions and a defined registration process for all products. Product sales are monitored and reported to an adverse effects registry. To minimize the uptake of electronic cigarette use by youth, the regulation includes a ban on the sales to minors below the age of 18. The Tobacco Products Directive is being continuously assessed with the goal of revising it every few years based on the monitoring process. The TPD, although not perfect, is realistic and largely applicable to any other country.

The UK has adopted a more aggressive approach in supporting electronic cigarettes in a tobacco harm reduction strategy. The National Institute of Clinical Excellence actively recommends that health care workers advice smokers about potential utility of e-cigarettes as smoking cessation modalities⁽³⁴²⁾, while the UK Parliament Science and Technology Committee recommended an even more liberal regulatory framework for e-cigarettes in order to further strengthen their effect as a smoking cessation measure⁽³⁴³⁾. These positions indicate the acceptability of current evidence on safety and efficacy of these products, and the valuable prospects of strengthening the tobacco control measures through a harm reduction strategy with e-cigarettes.

In that respect, regulatory initiatives for electronic cigarettes should follow 6 basic principles, presented in Table 11.



- a. Regulation for electronic cigarettes, including flavours, should be risk proportionate.** This represents the only proper approach to the regulation of any product. Evidence on risk determines the levels of restrictions that need to be implemented. As presented above, there is compelling evidence on the very low risk of electronic cigarettes, especially when compared with the devastating effects of smoking.
- b. Regulation for electronic cigarettes, including flavours, should be realistic and ensure product quality.** It would make little sense to create a regulation that would be expensive or difficult to comply. This would result in the elimination of electronic cigarettes and the creation of an uncontrolled black market. Both consequences will end-up protecting tobacco cigarette sales while no quality standards can be expected from black market products.
- c. Regulation should ensure that electronic cigarettes, including flavours, do not target never-smokers and youth.** This can be ensured by introducing a ban on the sales of electronic cigarettes to people below 18 years old (with heavy fines for those violating this rule), specific regulatory restrictions (but not ban) on advertising and marketing and proper education that electronic cigarettes should be used as smoking substitutes only.
- d. Regulation should create a competitive advantage for electronic cigarettes compared to tobacco cigarettes.** Flavours contribute towards consumer acceptance and should therefore not be excluded for adult smokers. Unfortunately, tobacco cigarettes are very cheap to make and generate a lot of profits for the industry. Electronic cigarettes are technology products; thus, they are by definition more expensive to produce than tobacco products. Regulation should ensure that smokers are motivated to switch to electronic cigarette use and completely quit smoking. Therefore, taxation policy should ensure that they are cheaper than tobacco cigarettes. Additionally, smokers should have easier access to electronic cigarette products than to tobacco cigarettes. Marketing and advertising bans should be implemented for tobacco cigarettes while regulated and carefully controlled marketing for electronic cigarettes is essential in order to target, inform and educate smokers about the existence and value of electronic cigarettes in improving their health. Products should contain enough nicotine; otherwise, smokers will continue to smoke in order to obtain the nicotine they need.
- e. Regulation should classify electronic cigarettes as consumer products with specific rules, safety standards and restrictions, including for flavours.** The success of electronic cigarettes as smoking substitutes is based on their use as consumer products. They are used according to smokers' preferences and needs, while product choice also depends on personal taste and preference. This can only be ensured through a regulatory framework of characterizing electronic cigarettes as consumer products with the restrictions mentioned above.

f. Regulation should allow innovation and development of better and even safer electronic cigarette products, including for flavours. Being technology products, electronic cigarettes have evolved at a rapid pace in recent years. Currently available products are safer and more effective as smoking substitutes than the products available a few years ago because of using better materials, providing a better experience for smokers and being more effective in alleviating smoking cravings.

Table 11: Regulatory perspectives on electronic cigarettes.

Regulatory rules	Rationale - evidence	Benefit
Classification		
Different classification for electronic cigarettes vs. tobacco cigarettes.	Electronic cigarettes do not contain any tobacco. Nicotine has minimal adverse health effects. The lack of combustion is a main determinant of the risk difference between tobacco cigarettes and electronic cigarettes.	It will be easier for smokers to understand the difference in function and risk between the products.
Different restrictions on electronic cigarette use vs. smoking.	Restrictions should be based on a risk continuum and be evidence based. For example, while banning smoking in closed public places is scientifically justified, current evidence suggests no substantial health harm from second-hand exposure to electronic cigarette aerosol.	Smokers will better understand the difference in risk between products and might be more motivated to quit by switching to electronic cigarette use.
Product quality		
Reasonable quality standards for electronic cigarette products.	While electronic cigarettes do not involve combustion, this cannot justify the liberal use of any chemical without considering known and potential risks. Standards should be reasonable and easy to comply, to avoid creating a monopoly (e.g., by big tobacco companies).	Ensure product quality for consumers, further minimize potential risks. The European Union model of setting quality standards could be used as a basis.
Registration of all products through a transparent and clearly defined process.	As any consumer product, regulation needs to clearly record the products that are available to consumers. The process will ensure compliance with all other regulatory decisions.	Avoid the creation of a "black market" and the marketing of products with questionable quality. Ensure that any new knowledge or information about problems or risks will be addressed through changes in the market (e.g., in case specific products need to be withdrawn from the market, for quality control, etc).
Availability, accessibility and promotion		
Controlled (but not banned) marketing so that only smokers are targeted.	Electronic cigarettes are intended to be used as smoking substitutes and not as a new "trendy" habit for anyone to adopt. Smokers need to be informed about the availability of these products and their potential advantages compared to tobacco cigarettes. Deliver a clear message that the best approach is for people to quit smoking without using any alternative product. Electronic cigarettes should supplement (and not substitute) all other tobacco control efforts.	Ensure that electronic cigarettes are appealing to smokers only and are not attractive to non-smokers. Allow smokers to make informed decisions about their health.



Ban on sales to youth (< 18 years old).

Increased accessibility of electronic cigarettes (e.g., allow online sales).

Packaging/labelling warnings on electronic cigarette products should be confined to the dependence potential of nicotine

Substantially reduced or (preferably) no taxation for electronic cigarettes

Ensure minimal access of youth to e-cigarettes.

While tobacco cigarettes are available everywhere and are easily accessible, sales points for electronic cigarettes are limited. Prohibition of online sales will limit accessibility to a harm reduction product. Such a prohibition unintentionally protects the sales of the most accessible and available product (i.e., tobacco cigarettes).

Health warnings are scientifically justified for tobacco cigarettes (and other combustible products). There is no scientific evidence on the introduction of warnings about health risks in electronic cigarettes. A warning about the dependence potential of nicotine is justified.

Financial incentives should be used to convince more people to switch from tobacco cigarettes to electronic cigarettes.

Prevent electronic cigarettes from being a new "trend" among youth.

Accessibility to electronic cigarettes will be facilitated, especially in remote areas. Accessibility to tobacco cigarettes should be limited.

Smokers will better understand the risk difference between products. People who do not want to develop dependence on nicotine will be warned against the use of nicotine-containing electronic cigarettes.

Reduced price will allow more smokers to afford electronic cigarettes.

11. CONCLUSIONS

a. **Flavours used in ENDS are inextricably linked to smoking cessation**

It is clear that flavoured nicotine vaping products are instrumental in aiding adult smokers in their quest to quit smoking cigarettes. In my view, legislators should seriously take this into account, especially when they start considering the regulation of flavour in ENDS.

b. **Bans of ENDS / flavours will harm, not help individual and population health**

Flavour bans equate to a form of prohibition, which is a net negative for society, both in terms of criminal activity and consumer safety. Moreover, the greatest risk is for bans to redirect vapers back to smoking deadly combustible cigarettes.

c. **Blocking youth initiation of smoking (and vaping) is a priority**

While youth access to vaping products is a serious problem, and one that needs to be addressed, it would be misguided to ban vaping flavours to attempt to accomplish the goal of eliminating youth use. Banning flavours would disproportionately harm adult smokers who are trying to quit, which is contrary to their fundamental human rights and right to access all beneficial healthcare options. Instead of bans and prohibition, it would be best if legislators focused more narrowly on youth access at the point of sale and to eliminate flavour descriptors clearly targeting the youth.

d. **Health professionals play an important role to provide accurate and evidence-based risk communication on ENDS and flavours.**

Tobacco control provided the insight that health professionals and in particular, medical doctors have tremendous influence in consumer choices. They can play a highly influential role in curbing tobacco use in any community. In fact, during the early part of the last century, doctors were the first to start smoking, but also the first social grouping to quit smoking. This was mostly due to the research of Dr Richard Doll, whose 1950 article [\[41\]](#) in the British



Medical Journal (BMJ) essentially started the tobacco control movement. In this article, he powerfully established the link between cigarette smoking in medical doctors and lung cancer.

Likewise, it is clear that where medical doctors take the lead and stop smoking themselves, advise patients to quit and advocate for policy change, sustained action follows.

Dr Derek Yach, former Executive Director at the World Health Organization (WHO) as well as the former President of the Foundation for a Smoke Free World, states that^[42]:

“physicians were, in fact, key to progress in the USA and OECD countries, where smoking rates have dropped steadily over the decades. In these countries, doctors’ smoking rates dropped and, within a decade, smoking rates fell in the general population. In many major LMICs, physician smoking rates remain extremely high. Correspondingly, doctors’ voices and advocacy are weak. Until this changes, progress will be slow.”

It is clear that future physicians and health leaders will depend on this generation to have made wise judgments and offered the right advice to the right patients at the right time. For the practicing physician today, the evidence is clear – build THR into your practice without delay!



12. RECOMMENDATIONS

a. Smoking Cessation Optimisation

The top priority for public health:

- 1,1 billion adult smokers can be provided with effective smoking cessation tools – including the use of flavours in the various regulated products
- Evidence shows that the harms of combustible tobacco use can be minimised or largely avoided if a person quits before entering middle age.
- Accurate risk communication is essential, as many tobacco users are confused with the misinformation and lack of risk-proportionate communication on proven cessation tools – especially tobacco harm-reduction (THR) products.
- More support is needed from national health communication campaigns, including health and educational authorities
- Misinformation about non-combustible, nicotine-based alternatives to combustible tobacco, should be stamped out. Risk perception studies in several parts of the world show that consumers believe e-cigarettes (ENDS) are as harmful as cigarettes. This needs to be rectified

RECOMMENDATION #1

Optimise efforts to increase the accessibility, affordability and consumer acceptance of smoking cessation products, such as flavoured nicotine vaping products (ENDS) – through proportionate, risk-based regulation and robust monitoring and evaluation of its use.

b. Consumer Understanding

The United Nations call for a “whole-of-society” approach to prevent and control tobacco-related non-communicable diseases. Consumers need to be given a voice in this debate. There are approximately 100 million consumers of smoke-free, reduced risk alternatives to combustible products. Most of these products are flavoured. If flavour bans are being considered, it is imperative to better understand the reasons why consumers prefer flavoured products, in order to switch away from, or quit cigarette smoking.

RECOMMENDATION #2

Conduct wide-ranging consumer perception and behavioural studies, to determine and help validate the role and effectiveness of flavours, to help adult smokers switch away from, or quit combustible cigarettes altogether.



c. **Research into the safety and quality of flavours in THR**

If flavours contribute to smoking cessation, this opportunity needs to be leveraged. Research to strengthen the role of flavours should include the verification of its safety and quality:

- Safety studies of flavours
- Quality assurance of flavours used in THR product
- Cross-industry studies to understand the role and regulation of flavours in other industries, e.g. the food & beverage and alcohol industries
- Multi-stakeholder engagement and a “whole-of-society” approach are needed to successfully use THR for the benefit of individual and population health. Some of the best research on THR products, including flavours, is being done in the tobacco and nicotine industries. Their research and consumer insights should be used appropriately, to contribute towards the evidence base for sound regulation

RECOMMENDATION #3

More funding and more research to ensure the safety and quality of flavours used in THR products, for effective tobacco cessation and harm reduction. This should include the sharing of relevant, non-proprietary research findings

d. **Role of Health Professionals in harm reduction and the role of flavoured nicotine vaping products (ENDS)**

Health professionals are in the front line, interfacing with consumers and especially adult smokers. Amongst these groups, there is still a critical lack of training and knowledge on nicotine, flavours, and the use of non-combustible nicotine alternatives, to either quit smoking or to switch to less harmful alternatives.

RECOMMENDATION #4

Monitor the health professional perceptions of THR products, including the role of flavours in smoking cessation

RECOMMENDATION #5

Upgrade the training of health professionals in THR science, policy and products, including the role of flavours (as is used in Nicotine Replacement Therapy)



e. Preventing Youth Initiation

The increased use of non-combustible alternative nicotine-delivery systems by youth should be avoided and addressed, for example:

- Bans at points of sale
- Marketing bans, for those marketing practices clearly targeting the youth.
- Research on proven policies to minimise marketing to children, as has been developed in the food & beverage industry, with independent monitoring and evaluation

RECOMMENDATION #6

Development of marketing codes / guidelines and pressure on multi-national and small, medium enterprises to commit to the highest possible standards, to restrict marketing to children / youth, along with independent non-industry led monitoring and evaluation of compliance to commitments. More importantly, capacity building to aid the enforcement of these regulations.

f. Advocating for Risk-Proportionate Regulation of THR and Flavours

For THR products, including flavoured products, to effectively maximise smoking cessation, proportionate and balanced regulation is needed:

- Evidence is growing in countries where such regulation is in place – the United Kingdom, New Zealand, France, Japan, South Korea and Sweden – tobacco-related disease and premature death are decreasing. This potential needs to be leveraged by all 194 member states of WHO

RECOMMENDATION #7

Critical need for the advocacy for and establishment of risk-proportionate, balanced regulations of tobacco harm reduction products, including the use of flavours.



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His field of expertise is Public Health. He has been conducting laboratory, clinical and epidemiological research on smoking, tobacco harm reduction and nicotine products as principal investigator since 2011. He authored the first systematic review on e-cigarette safety/risk profile, published in 2014. Additionally, he has performed research and published studies on heated tobacco products. His findings have been presented in major international scientific congresses and his studies were used in preparing the regulatory framework on e-cigarettes by the European Union. As of mid-2021, he has published approximately 100 studies and articles in international peer-reviewed scientific journals about smoking, tobacco harm reduction and alternative-to-smoking nicotine products. He was the handling editor and author of a book titled "Analytical assessment of e-cigarettes", published by Elsevier in 2017. In November 2020, he was declared a Highly Cited Researcher 2019 by the Web of Science, a list of researchers (6200 scientists out of 9 million examined) with the highest impact in global science in 21 scientific fields in the past decade. During the COVID-19 pandemic, he has published 8 peer-reviewed studies and several pre-prints about the COVID-19, including the association between smoking, nicotine and COVID-19.

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