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COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Paper for Information: Potential toxicological risks from electronic nicotine (and non-nicotine) delivery systems (E(N)NDS – e-cigarettes). Reviews by UK and International organisations.

Background

1. On request from PHE, the COT has reviewed the potential toxicological risks from electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS) (collectively abbreviated to E(N)NDS). The main perspective of the COT review was to evaluate the risk from use of E(N)NDS as an aid to cessation of smoking conventional cigarettes (CC).

2. This paper for information provides an overview of the opinions of authoritative bodies throughout the world regarding the risk of E(N)NDS use, health effects of nicotine, particulate matter (PM), propylene glycol (PG) and glycerol (vegetable glycerine (VG)), flavouring compounds and degradation products, other constituents and bystander exposure. Where no data have been given in this report, this indicates that the authoritative body did not provide any data or an opinion about the topic.

Introduction

3. E(N)NDS are battery-powered devices containing a liquid (E(N)NDS liquid or ‘e-liquid’). The E(N)NDS liquid is heated on use to produce an aerosol that is inhaled by the user (‘puffing’, ‘vaping’). E(N)NDS were first introduced commercially in China in 2004 and subsequently in the European Union (EU, 2005) and United States of America (USA, 2007) as nicotine-delivery devices (Bansal & Kim, 2016). The main constituent parts of an E(N)NDS device are a mouthpiece, cartridge (tank) containing E(N)NDS liquid, a heating element/atomizer, a microprocessor, a battery, and sometimes a light-emitting diode (LED) light. Commercially available devices are sometimes categorised as first, second, or third generation. First-generation devices look like conventional cigarettes (CCs) and thus are termed ‘cigalikes’. Initial models comprised three principal parts; a lithium-ion battery, a cartridge and an atomizer. However, more recent models mostly consist of a battery connected to a ‘cartomizer’ (cartridge/atomizer combined), which may be replaceable, but is not refillable. Second-generation E(N)NDS are larger and have less resemblance to tobacco cigarettes. They often resemble pens or laser pointers (hence the name, ‘vape pens’). They have a high-capacity rechargeable lithium-ion battery and a refillable

atomizer (sometimes referred to as a 'clearomizer'). Third-generation models ('advanced personal vapers', 'mods') are also refillable, have very-high-capacity lithium-ion batteries and are highly customisable (different coil options, power settings, tank sizes). In addition, highly advanced 'fourth generation' E(N)NDS (innovative regulated mods) are now being described.

Search strategies

4. Websites of authoritative bodies were interrogated for opinions and conclusions on the risk of E(N)NDS use, including the inhalation toxicity of E(N)NDS, their constituents and potential degradation products. Authoritative bodies included World Health Organization (WHO), Public Health England (PHE), National Institute for Public Health and the Environment (RIVM) in The Netherlands, US National Academies of Sciences, Engineering and Medicine (NAS), Federal Institute for Risk Assessment (BfR) in Germany, the New Zealand Ministry of Health, the Australian National Health and Medical Research Council (NHMRC), National Industrial Chemicals Notification and Assessment Scheme (NICNAS) and Department of Industry, Innovation and Science and French Agency for Food, Environmental and Occupational Health & Safety (ANSES). Moreover, opinions from a number of societies were also sought, including Forum of International Respiratory Societies, Tobacco Advisory Group of the Royal College of Physicians (RCP), Royal College of General Practitioners (RCGP) and European Respiratory Society (ERS).

World Health Organization

World Health Organization (2016a)

5. The WHO was invited to prepare a report on E(N)NDS by the Conference of the Parties (COP), covering updates on the evidence of the health impact of E(N)NDS, their potential role in tobacco cessation and impact on tobacco control efforts; and subsequently to assess policy options to achieve the objectives outlined in paragraph 2 of decision FCTC/COP6(9)[1]; and consider the methods to measure the contents and emissions of these products (WHO, 2016). The main points and conclusions are summarised below.

Risk of E(N)NDS

6. Based on the number and concentration of toxicants produced during the typical use of E(N)NDS made with pharmaceutical-grade ingredients, WHO

1 Electronic nicotine delivery systems and electronic non-nicotine delivery systems. The COP invites Parties, when addressing the challenge posed by ENDS/ENNDS, to consider taking measures such as those referred to in document FCTC/COP/6/10 Rev.1 in order to achieve at least the following objectives, in accordance with national law:(a)prevent the initiation of ENDS/ENNDS by non-smokers and youth with special attention to vulnerable groups;(b)minimize as far as possible potential health risks to ENDS/ENNDS users and protect non-users from exposure to their emissions;(c)prevent unproven health claims from being made about ENDS/ENNDS; and(d)protect tobacco-control activities from all commercial and other vested interests related to ENDS/ENNDS, including interests of the tobacco industry

concluded that it is likely that E(N)NDS are less toxic than cigarette smoke. However, E(N)NDS are unlikely to be harmless, and long-term use is expected to increase the risk of chronic obstructive pulmonary disease (COPD), lung cancer and, potentially, cardiovascular disease. The risk of other diseases also associated with smoking may also be increased. The magnitude of such risks is likely to be smaller than from CC smoke, although WHO noted that there is not enough research to quantify the relative risk of E(N)NDS over combustible products. WHO concluded that 'no specific figure about how much safer the use of ENDS/ENNDS is compared to smoking can be given any scientific credibility. However, it was noted that existing modelling studies indicate that in order for there to be a population-wide net health benefit from ENDS/ENNDS, based on present usage rates, ENDS/ENNDS products would need to be at least three times safer than cigarettes' (WHO, 2016).

7. WHO also noted that there was urgent need to elucidate the range of relative risks when using E(N)NDS devices and e-liquids, and to understand user behaviour compared with smoking and use of other nicotine products, recognizing that:

- complex mixtures, such as in E(N)NDS liquids and aerosol, have the potential for toxicological effects even if toxicants are at low or very low concentrations
- predicting adverse health effects of these complex mixtures solely on aerosol composition may be unsuccessful without solid evidence from chemical, *in vitro*, clinical and epidemiological methods; and that
- simple comparisons of toxicant concentrations in E(N)NDS aerosol to the high levels in tobacco smoke, may be of little value given the absence of science on safe tolerance limits for smoke constituents or their specific effects on the multiple diseases caused by smoking.

8. In the appendix to the report, WHO cited other health risks that should be considered, including the simultaneous use of E(N)NDS and combustible tobacco products. There is debate whether dual use of E(N)NDS and CC translates to fewer cigarettes smoked and therefore a lower intake of smoke toxicants, and if, ultimately, dual users quit smoking and switch entirely to E(N)NDS. WHO noted that "Dual use may lead to some reduction on number and duration of smoking, depending on the degree of substitution and age of initial dual use with all other factors - user behavior, type of ENDS and eliquids – being equal. However, its translation into reduction of lifetime risk it is not expected to be significant. Initial data on the impact of reduce cigarette consumption might have raised some hope. Nevertheless, the most recent data indicates that reduction of smoking reduces very little if any the lifetime risk".

Nicotine

9. Aerosol from ENDS contains nicotine which is well known to be addictive. As well as dependence, nicotine may also cause developmental effects on the fetus during pregnancy and may contribute to cardiovascular disease. Although nicotine is

not a carcinogen, it may also function as a “tumour promoter” and appears to be involved in the progression of malignant diseases, as well as of neurodegeneration.

10. Long-term consequences for brain development may occur following fetal and adolescent nicotine exposure, which may potentially lead to learning and anxiety disorders. WHO notes that the evidence is sufficient to warn children and adolescents, pregnant women, and women of reproductive age against ENDS use and nicotine.

Flavourings and their degradation products

11. The health effects of heated and inhaled flavouring compounds used in in e-liquids have not been well studied. WHO stated that heated and inhaled flavours, including popcorn, cinnamon and cherry are potentially hazardous. The limited literature indicates that most flavours may pose appreciable health risks from long-term use, especially sweet flavours. Many flavouring compounds are irritants, which may increase airway inflammation. Some flavoured aerosols are also more cytotoxic compared with unflavoured aerosols, although less so than compared with tobacco smoke.

Other constituents and products formed on aerosolization

12. The number and level of known toxicants generated by typical use of unadulterated E(N)NDS is, on average, lower than in CC smoke. However, the levels of toxicants vary between brands of E(N)NDS and may, in some cases, reach higher levels than in CC smoke. This is due to increased thermal decomposition of e-liquid ingredients, the possibility for heating elements and other components to shed metals and other particles, and the use of different analytical techniques. WHO noted that few techniques have been standardised and validated for analysing E(N)NDS.

13. Various metals, including lead, chromium, and nickel, have also been found in the aerosol of some E(N)NDS at concentrations equal to or greater than CCs under typical use conditions.

Bystander exposure

14. WHO noted that a systematic review on the health risks from passive exposure to exhaled aerosol from E(N)NDS users or second-hand aerosol, carried out by Hess et al., (2016)[2], concluded that the ‘absolute impact from passive exposure to electronic cigarette vapour has the potential to lead to adverse health effects’.

15. Subsequently, a WHO-commissioned review carried out by Fernandez et al.[3] in 2016, noted that second-hand aerosol is a new air contamination source for PM, including fine and ultrafine particles as well as PG, volatile organic compounds

2 Hess I, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. Public Health Research & Practice. 2016;26(2).
3 Fernandez, E., et al , Institut Català d’Oncologia, Exposure to Aerosols from Smoking-proxy Electronic Inhaling Systems: a Systematic Review, unpublished report, (2016)

(VOCs), heavy metals and nicotine, although there are limited data available. Except for the heavy metals, the concentrations of these compounds are generally lower in second-hand aerosol than in second-hand CC smoke. WHO concluded that 'at present, the magnitude of health risks from higher than background levels of these compounds and elements are empirically unknown'.

World Health Organization (2016b)

16. WHO commissioned Fernandez et al. to carry out a systematic review to evaluate exposure of bystanders to second-hand aerosol (Fernandez, Fu, & Martinez-Sanchez, 2016). The main points and conclusions are summarised below.

Bystander exposure

17. Authors of the systematic review concluded that 'second-hand aerosol is primarily from exhaled first-hand aerosol'. Bystanders are exposed to chemicals present in second-hand aerosol as shown by cotinine measurements. The content and concentrations of chemicals in first-hand aerosol is highly variable depending on the type of device used, the composition of e-liquid and a variability in usage parameters.

18. Second-hand aerosol is a significant source of exposure of bystanders. The concentrations of formaldehyde present in second-hand aerosol would pose an excess lifetime cancer risk between 270 and 720 per million and of acetaldehyde an excess lifetime cancer risk between 4 and 360 per million. Second-hand aerosol also increases fine and ultrafine particle concentrations in ambient air and is also a potential hazard to bystanders. Other chemicals identified in second-hand aerosol include polycyclic aromatic hydrocarbons (PAHs), tobacco specific nitrosamines (TSNAs), acrolein and metals such as copper, cadmium, nickel and lead.

19. Overall, authors concluded that second-hand aerosol is a new indoor air contamination source of PG, PM, including fine and ultrafine particles, VOCs, metals and nicotine. However, except for metals, such compounds have lower concentrations than found in second-hand CC smoke. The implications of short- and long-term health risks remain unknown (Fernandez et al., 2016).

World Health Organization (2015)

20. A systematic review of the health effects of E(N)NDS was carried out by Pisinger on behalf of WHO (Pisinger, 2015). The main points and conclusions are summarised below.

Risk of E(N)NDS

21. Following the systematic review, the author stated that 'even though no firm conclusions can be drawn on the safety of e-cigarettes there is an increasing body of evidence indicating harm'. For ex-smokers and never smokers, use of e-cigarettes will increase the risk of harm to health. Effects on the pulmonary system, cardiovascular system and carcinogenic effects cannot be ruled out'.

Particulate matter

22. A number of studies investigated particles in E(N)NDS aerosol. One study found that e-liquid generated nanoparticles up to 3000 times more than found in ambient air. Particles measured in E(N)NDS aerosols and CC smoke were reported to be of comparable sizes by some studies, although one study reported that E(N)NDS aerosols contained smaller particles compared with CC smoke and another study reported larger particle sizes.

23. Assessment of indoor air quality showed that there were high concentrations of ultrafine particles ($PM_{2.5}$) following vaping sessions, although the concentrations were lower than from CC smoking.

Propylene glycol and glycerol

24. Propylene glycol and VG are recognised as safe for oral intake and concentrations found in E(N)NDS liquids are typically below occupational standards. It was noted by the authors that occupational safety standards are not intended to establish safe exposure concentrations for the general population but to reduce harm in exposed workers during the working day. Moreover, inhalation and ingestion may not result in the same toxic effects. The authors cited an internal technical report that concluded the 'estimated levels of exposure to propylene glycol and glycerol are close to the threshold limit values to warrant concern'.

25. The systematic review identified several animal studies carried out with PG. Such studies showed an inhalation of PG increased number of goblet cells in the respiratory tract and nasal hemorrhaging, irritation to the upper respiratory tract and squamous metaplasia of the epiglottis following exposure at concentrations present in E(N)NDS. Exposure in humans caused ocular irritation, airway obstruction and dyspnoea, and exacerbation or induction of allergic symptoms in children.

Nicotine

26. Nicotine has significant biological activity. It stimulates the release of neurotransmitters and hormones in the central nervous system and peripheral nervous system, and stimulates the release of catecholamine, causing vasoconstriction, increased heart rate and myocardial contractility. In *in vitro* systems, data indicate potential direct carcinogenic and genotoxic effects of nicotine, although it has not been classified by the International Agency on the Research on Cancer (IARC).

27. Both human and animal data indicate that nicotine exposure during periods of developmental vulnerability may cause adverse health effects including impaired foetal brain and lung development and altered brain development in adolescents.

Flavourings and their degradation products

28. The report noted a recent study that concluded that concentrations of some flavouring chemicals in e-liquids are sufficiently high for inhalation exposure to be of

toxicological concern. A number of studies identified in the systematic review also reported flavouring compounds to be associated with potential harm. Authors noted that generally recognised as safe (GRAS) applies only to oral intake, that flavour ingredients are only evaluated for use in food, and that the GRAS status does not mean that flavour ingredients are safe for use in E(N)NDS.

Other constituents and products formed on aerosolization

29. A few studies reported that concentrations of lead and chromium in E(N)NDS aerosol were similar to those reported in CCs, except that nickel that was 100-fold higher than CCs. One puff produced aerosol that contained metal particles including silver, nickel, aluminium, chromium and nickel; the latter were present as nano particles. One study compared levels of metals with regulatory standards and concluded that levels of metals were unlikely to generate significant adverse health effects for smokers switching to E(N)NDS use (Pisinger, 2015).

Bystander exposure

30. Several human experimental studies have indicated that bystander exposure resulted in short-term lung obstruction and increased cotinine. However, passive vaping did not affect blood count in ex- or never smokers. Further studies found that non-smoking bystanders passively exposed to E(N)NDS aerosol absorbed approximately the same amount of nicotine as when exposed to CC smoke.

World Health Organization (2014)

31. In 2014, the WHO was invited to examine emerging evidence on the health effects of E(N)NDS, in response to the request made by the COP. The report incorporated scientific recommendations by the WHO Study Group on Tobacco Product Regulation and analysis from the recent WHO survey on tobacco products (WHO, 2014). The main points and conclusions are summarised below.

Risk of E(N)NDS

32. The report made a number of statements regarding the health effects of E(N)NDS. The aerosol usually contains carcinogenic compounds and other toxicants found in tobacco smoke at levels of 1–2 orders of magnitude lower than in CC smoke. For some brands, the level of some of these carcinogens, such as formaldehyde and acrolein, are as high as in CC smoke. It is likely that average E(N)NDS use produces lower exposure to toxicants compared with combustible products.

33. Overall, the existing evidence shows that E(N)NDS aerosol may pose a risk to adolescents and fetuses. It also increases exposure of non-smokers and bystanders to nicotine and several other toxicants. However, exposure to E(N)NDS is likely to be less toxic compared with CCs. The amount of risk reduction, however, is presently unknown.

Particulate matter

34. The WHO report concluded that the range and size of particles delivered by E(N)NDS is similar to that of CCs, with most particles being in the ultrafine range (100–200 nm), compared to larger particles found in CC smoke. However, E(N)NDS generate lower level of particles than CC.

Propylene glycol and glycerol

35. Short-term effects of E(N)NDS include eye and respiratory irritation caused by exposure to PG. Serious short-term health problems may occur but are very rare.

Nicotine

36. Nicotine is the addictive component of tobacco. It can have adverse effects during pregnancy and can contribute to cardiovascular disease. Although it is not carcinogenic, it may act as a tumour promoter. Nicotine is involved in a number of malignant diseases, as well as neurodegeneration.

37. Overall, WHO noted that 'evidence is sufficient to caution children and adolescents, pregnant women and women of reproductive age about ENDS use because of the potential for foetal an adolescent nicotine exposure to have long term consequences for brain development'.

Flavourings and their degradation products

38. Authors stated that assessment of the flavouring chemicals in e-liquids and E(N)NDS aerosols indicate potential cytotoxicity of some e-liquids, related to the concentration and number of flavourings present. This raises concerns about pregnant women who use E(N)NDS or are exposed to second-hand E(N)NDS aerosol.

Bystander exposure

39. Regarding bystanders, the WHO report noted that bystanders are exposed to aerosol exhaled by E(N)NDS users, which increases background level of some toxicants, nicotine, fine and ultrafine particles in the air. However, levels of toxicants emitted from E(N)NDS are lower than that emitted from CCs. It is unknown if exposure to toxicants and particles in exhaled aerosol will lead to an increased risk to health among bystanders. However, some studies show adverse effects of PM from any source following short- and long-term exposures.

World Health Organization (2013)

40. In 2013, a background paper on E(N)NDS was prepared by Grana et al. for the WHO Tobacco Free Initiative by the WHO Collaborating Centre on Tobacco Control (Grana, Benowitz, & Glantz, 2013). The main points and conclusions are summarised below.

Risk of E(N)NDS

41. In the executive summary of the report, authors concluded that ‘e-cigarettes deliver lower levels of toxins than CCs, but they still deliver some toxins. E-cigarettes pollute the air less than CCs, but they pollute the air. They do not just emit "harmless water vapor”. They also noted that there is little research on direct health effects, citing one study that shows short-term pulmonary effects, and noting cytotoxicity in animal and human *in vitro* test systems.

42. Overall, WHO concluded that the available studies provide a very limited perspective on the health effects of E(N)NDS. Few products in a limited number of studies have been tested, although some do indicate that E(N)NDS aerosol exposure could result in biological effects. However, long term effects are unknown as E(N)NDS have not been in widespread use long enough to assess these effects.

Particulate matter

43. A number of studies that measured the diameter of particles comprising E(N)NDS aerosol reported that small (<10 µm in diameter), fine (<2.5 µm) and ultrafine/nanoparticles (<1 µm) are present. Particle size distribution and the number of particles delivered by E(N)NDS is similar to that of CCs, with most being in the ultrafine range. Users exhale some of these particles thereby exposing bystanders, known as passive vaping. As with CCs, particles from E(N)NDS are small enough to reach the lung and enter the systemic circulation.

44. WHO concluded that based on the available data, it is expected that E(N)NDS aerosol could be inhaled into the lungs similarly to CCs and particle concentrations were similar. Moreover, E(N)NDS have much lower levels of most toxicants, although not particles, compared with CCs. The thresholds for human toxicity in E(N)NDS aerosol are not known and the possibility of health risks to users, as well as bystanders, must be considered.

Propylene glycol and glycerol

45. Based on a material safety data sheet, WHO noted that PG can cause respiratory irritation and prolonged or repeated inhalation may affect behaviour and cause central nervous system effects. When heated and vaporised, PG can form propylene oxide, which has been classified by IARC as a category 2B carcinogen, and VG can form acrolein, which can cause upper respiratory tract imitation.

Nicotine

46. The WHO report did not cover the toxicity of nicotine. However, they noted that the early studies of nicotine absorption found that E(N)NDS delivered a lower level of plasma nicotine compared with CCs, whilst more recent studies demonstrated that experienced users can achieve nicotine absorption similar to that of cigarettes.

Other constituents and products formed on aerosolization

47. Authors identified a number of studies that analysed constituents of e-liquids and aerosols. Most showed the presence of carbonyls, VOCs and TSNAs. The levels of toxicants in the aerosol were 9-450 times lower than in CC smoke supporting the idea that E(N)NDS aerosol is less hazardous (Grana et al., 2013).

Bystander exposure

48. WHO cited a paper by Burstyn (2013)[4] that stated that 'there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (contaminants plus declared ingredients), if it were an emission from industrial process, creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less and does pose no apparent concern'.

49. In contrast, based on the study that assessed the short-term effects of active and second-hand E(N)NDS and CC use on serum cotinine and pulmonary function, it was concluded that with very heavy passive exposure there is also similar systemic exposure to nicotine from tobacco and E(N)NDS among bystanders.

UK

Public Health England (2019)

50. Following a report published in 2018, a second report was commissioned by PHE to summarise evidence to underpin policy and regulation of E(N)NDS in England (McNeill, Brose, Calder, Bauld, & Robson, 2019). The report focuses mainly on the latest evidence on prevalence and characteristics of E(N)NDS use in young people and adults in England but does not include potential adverse health effects or toxicity of E(N)NDS.

Public Health England (2018)

51. In 2018, PHE commissioned a study to summarise evidence to underpin policy and regulation of E(N)NDS (McNeill, Brose, Bauld, & Robson, 2018) as an update to their 2015 report. The main points and conclusions are summarised below.

Risk of E(N)NDS

52. The report made a number of key findings regarding the health risks of E(N)NDS. Authors noted that the main carcinogens and toxins that are inhaled by CC smokers have also been detected in smokers who switched to E(N)NDS albeit at much lower levels. Indeed, biomarkers of exposure are consistent with significant

4 Burstyn, I., 2013. Peering through the mist: What does the chemistry of contaminants in electronic cigarettes tell us about health risks?

reductions in harmful constituents and for a few biomarkers such as acrolein, levels in E(N)NDS users were similar to smokers abstaining from smoking or non-smokers.

53. The comparative risks of cardiovascular disease and lung disease have not been quantified but are also likely to be lower than the risks of smoking CCs.

54. Adolescents who used E(N)NDS reported more respiratory symptoms than those who did not use E(N)NDS. Some small or uncontrolled studies have noted improvements in asthma and in respiratory infections in CC smokers who switched to E(N)NDS use, but more research is needed.

Propylene glycol and glycerol

55. Although E(N)NDS can release high levels of aldehydes if the e-liquid is overheated, the authors noted that overheating generates an aversive taste that ensures that such emissions are minimised. At temperatures of typical use, aldehyde content in E(N)NDS aerosol is lower than levels in CC smoke.

Nicotine

56. The long-term local effects of nicotine on the lungs from E(N)NDS use is not yet understood and may be different from its systemic effects.

57. While nicotine could theoretically cause adverse health effects, long-term use of nicotine by 'snus'[5] users, at systemic concentrations seen in CC smokers and E(N)NDS users, has not caused serious health effect in adults, and use of nicotine replacement therapy by pregnant smokers has not increase risks to the fetus.

Flavourings and their degradation products

58. Authors noted that whilst there is no clear evidence that specific flavourings pose adverse health risks, it is suggested that 'inhaled chemicals in some flavourings could be a source of preventable risks'. Authors suggested that further research on the presence and effects of inhaled flavourings is warranted.

Other constituents and products formed on aerosolization

59. The report concluded that the 'levels of metals identified in e-cigarette aerosol do not give rise to any significant safety concerns but metal emissions, however small, are unnecessary'. E(N)NDS that generate minimal metal emissions should become an industry standard.

Bystander exposure

60. The report stated that there have been no identified health risks of passive vaping to bystanders. Moreover, it was noted that 'reporting of some academic studies has been misleading'.

5 A low nitrosamine form of smokeless tobacco

The Netherlands

National Institute for Public Health and the Environment (2015)

61. A risk assessment of E(N)NDS use was carried out by Visser et al. for the National Institute for Public Health and the Environment (RIVM) in the Netherlands (Visser et al., 2015). Authors identified a number of factors that influence exposure to substances due to E(N)NDS use, including concentrations of chemicals in the inhaled aerosol, duration of exposure, frequency of exposure events (vaping sessions) and frequency of inhalation during vaping sessions.

Risk of E(N)NDS

62. A risk assessment was carried out based on the aerosol concentration data for two e-liquids. The e-liquids were chosen as aerosol concentrations were available for all substance groups (polyols, nicotine, aldehydes/ketones, TSNAs and VOCs).

63. E-liquids resulted in exposure to polyols (PG, VG, diethylene glycol and triethylene glycol), nicotine and TSNAs (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), N′-nitrosonornicotine (NAT)). Aldehydes (formaldehyde and acrolein) were also detected in the aerosol as degradation products formed during heating of the e-liquid. Authors concluded that the aldehyde concentrations in the aerosol were probably attributable to factors other than the nature of the e-liquid used and not therefore associable with the specific e-liquid.

64. Authors stated that in heavy vapers, there is a high risk of damage to the respiratory tract due to exposure to polyols; the concentration of PG was sufficient to pose a risk of systemic effects (reduced lymphocyte count); exposure to nicotine may induce effects on the respiratory tract and possibly systemic effects (effects on the cardiovascular system, fertility, a developing fetus); and exposure to NNK and NAT will increase the risk of tumour development in the respiratory tract. However, such risks could not be properly assessed due to a lack of appropriate data. Authors made no definitive conclusions regarding light and average E(N)NDS users.

65. Authors noted that there is a risk of effects on the respiratory tract following exposure to PG and VG vapour and it is likely that both damage the respiratory epithelium via the same mechanism. Therefore, cumulative effects of combined exposures to several polyols in e-liquid aerosol should be considered, as the overall risk from exposure to an e-liquid aerosol is significantly greater compared with individual components.

66. Overall, authors concluded that the health risks associated with smoking CCs are considerably higher than those associated with using E(N)NDS, although daily use of E(N)NDS is not without health risk. Exposure to polyols can damage the respiratory epithelium and reduce lymphocyte counts; nicotine can affect health in various ways, although no further information is provided; and TSNAs can increase the risk of tumour development. The presence of aldehydes is sufficient to induce

effects on the respiratory system and is thought to be due to the heating process rather than being present in e-liquids.

Propylene glycol and glycerol

67. The concentrations of PG and VG were measured in E(N)NDS vapour and from CCs. Concentrations of PG (17x) and VG (25x) were higher in E(N)NDS aerosol compared with CCs.

Nicotine

68. Following an investigation of 183 e-liquids available on the Dutch market, authors concluded that the nicotine concentration deviated by more than 10% from concentrations stated on packaging in 37% of e-liquids. In most cases actual concentrations were lower but in some cases, nicotine-free e-liquids did contain nicotine (Visser et al., 2015).

69. Measurements carried out to assess the constituents in E(N)NDS aerosol showed that nicotine was almost completely vaporised. In addition, its concentration in aerosol is dependent on the power output of the vaporiser and user behaviour.

Other constituents and products formed on aerosolization

70. The concentrations of TSNAs, aldehydes, VOCs and the metals cadmium and lead were measured in E(N)NDS aerosol and CC smoke. Concentrations of acrolein (4x), acetaldehyde (35x), TSNA, metals (cadmium (155x) and lead (3.5x)) and VOCs (benzene (40x) and toluene (1500x)) were lower in E(N)NDS aerosol compared with CC. Conversely, concentrations of formaldehyde (3x) were higher in E(N)NDS aerosol.

71. Formaldehyde, acetaldehyde and acrolein were not present in e-liquids but were present in aerosol due to being formed during heating. Formaldehyde and acrolein were present in concentrations sufficient to cause potential damage to the respiratory epithelium, which can be a precursor to tumour formation. Authors suggested that if the aerosol also contains acetaldehyde, acrolein and diacetyl in concentrations sufficient to damage the respiratory tract, the risk of formaldehyde-related tumours would be increased.

Germany

Federal Institute for Risk Assessment (2012a)

72. The BfR in Germany published an opinion that assessed the health effects of typical ingredients of e-liquids. The document in only available in German with only a summary being available in English (BfR, 2012b). The main points and conclusions are summarised below.

Risk of E(N)NDS

73. The BfR opinion stated that 'smokers of e-cigarettes do not inhale the characteristic carcinogenic combustion products and substances known to be present in tobacco smoke. Nevertheless, e-cigarettes cannot be considered safe with respect to health effects. Some pharmacological effects of nicotine – such as increased blood pressure and accelerated heart frequency, excessive production of gastric acid, increased adrenaline release – are often discussed as being associated with chronic diseases. In the future but not yet it might be possible to reliably assess the long-term health effects of e-cigarette'.

Propylene glycol and glycerol

74. Propylene glycol can lead to irritation of the upper respiratory tract and therefore may affect lung function. Little is known about the long-term effects of chronic exposure to PG.

Nicotine

75. Regarding nicotine, the BfR opinion stated that 'an important risk factor is posed by inhaling nicotine. Some pharmacological effects of nicotine, such as increased blood pressure and accelerated heart frequency, excessive production of gastric acid, increased adrenaline release, are often discussed as being associated with chronic diseases'.

76. Another potential risk factor of E(N)NDS is acute nicotine poisoning in adults through excessive use of E(N)NDS or in children as a result of accidental ingestion of the liquids (e.g. swallowing). E(N)NDS may also trigger nicotine dependency which might subsequently facilitate smoking of tobacco.

Other constituents and products formed on aerosolization

77. The BfR assessment stated that additional ingredients added to e-liquids such as chemical additives, pharmacologically active compounds, scent and aroma substances (e.g. menthol, linalool) and contaminants can pose a risk to health. In addition, there are indications in the literature that some E(N)NDS brands release carcinogenic aldehydes.

Bystander exposure

78. Based on the knowledge at the time, BfR concluded that the risks for bystanders (passive vapers) cannot be ruled out. Considering a wide range of e-liquids as well as the unlimited possibilities for mixing e-liquids, the nature of the substances that are inhaled and exhaled are often unclear. It is therefore difficult to identify pollutants that contribute to the contamination of indoor air. The BfR recommends that E(N)NDS should be treated like CCs in non-smoking areas and that use is banned in such zones.

Federal Institute for Risk Assessment (2012b)

79. The BfR also published a short document on their website regarding the health risks in passive vapers (BfR, 2012a). The main points and conclusions are summarised below.

Bystander exposure

80. The BfR assessed some typical substances present in e-liquids such as nicotine, fumigation agents (PG and glycerol), additives and flavouring chemicals and noted that aerosol from these substances can be detrimental to the health when inhaled by E(N)NDS users. In addition, risks for bystanders cannot be excluded. It was noted that a generalized risk assessment for bystanders remains difficult in individual circumstances. It was suggested that to provide an adequate protection for non-vaping bystanders, E(N)NDS should be treated equally to conventional tobacco products in smoke-free areas so they cannot affect the health of bystanders. For this reason, the BfR recommends that use of all E(N)NDS is to be banned in smoke-free areas. Even in private homes, E(N)NDS should be handled like normal cigarettes, i.e. they should not be used in the presence of sensitive persons such as children, pregnant women and sick persons.

France

81. The Tobacco and Vaping Products Working Group of ANSES does not appear to have any documents related to toxicological effects of E(N)NDS on their website.

USA

US National Academies of Sciences, Engineering, and Medicine

Risk of E(N)NDS

82. The NAS conducted a comprehensive scientific review to inform understanding of the public health impact of nicotine containing E(N)NDS devices (NAS, 2018). The Committee made a number of conclusions in relation to human health effects, as outlined below.

83. There is conclusive evidence:

- that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels
- that exposure to nicotine from e-cigarettes is highly variable and depends on product characteristics (including device and e-liquid characteristics) and how the device is operated
- that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances

- that other than nicotine, the number, quantity, and characteristics of potentially toxic substances emitted from e-cigarettes are highly variable and depend on product characteristics (including device and e-liquid characteristics) and how the device is operated
- that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis
- that intentionally or unintentionally drinking or injecting e-liquids can be fatal.

84. There is substantial evidence:

- that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes
- that e-cigarette aerosol contains metals. The origin of the metals could be the metallic coil used to heat the e-liquid, other parts of the e-cigarette device, or e-liquids. Product characteristics and use patterns may contribute to differences in the actual metals and metal concentrations measured in e-cigarette aerosol
- that e-cigarette aerosols can induce acute endothelial cell dysfunction, although the long-term consequences and outcomes on these parameters with long-term exposure to e-cigarette aerosol are uncertain
- that components of e-cigarette aerosols can promote formation of reactive oxygen species/oxidative stress. Although this supports the biological plausibility of tissue injury and disease from long-term exposure to e-cigarette aerosols, generation of reactive oxygen species and oxidative stress induction is generally lower from e-cigarettes than from combustible tobacco cigarette smoke
- that e-cigarette use results in symptoms of dependence on e-cigarettes
- that heart rate increases shortly after nicotine intake from e-cigarette
- that some chemicals present in e-cigarette aerosols (e.g., formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined
- that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems.

85. There is moderate evidence:

- that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes
- that diastolic blood pressure increases shortly after nicotine intake from e-cigarette
- that e-cigarette use results in increased cough and wheeze in adolescents, and an association between e-cigarette use and an increase in asthma exacerbations.

86. There is limited evidence:

- that the number of metals in e-cigarette aerosol could be greater than the number of metals in combustible tobacco cigarettes, except for cadmium, which is markedly lower in e-cigarettes compared with combustible tobacco cigarette
- that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control
- that in vivo animal studies using intermediate biomarkers of cancer support the hypothesis that long-term e-cigarette use could increase the risk of cancer. There is no available evidence from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk
- that e-cigarette aerosol can be mutagenic or cause DNA damage in humans, animal models, and human cells in culture
- for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use)
- of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies
- that e-cigarette exposure results in adverse effects on the respiratory system from animal and in vitro studies
- that nicotine and non-nicotine containing e-cigarette aerosol can adversely affect cell viability and cause cell damage of oral tissue in non-smokers
- that switching to e-cigarettes will improve periodontal disease in smoker

87. There is insufficient evidence:

- that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function
- whether or not maternal e-cigarette use affects foetal development

- that e-cigarette use changes short-term adverse health outcomes in several organ systems in smokers who continue to smoke combustible tobacco cigarettes (dual users)

88. There is no evidence:

- whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification)
- whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products
- whether or not e-cigarettes cause respiratory diseases in humans
- whether or not e-cigarettes affect pregnancy outcomes
- whether or not long-term e-cigarette use among smokers (dual use) changes morbidity or mortality compared with those who only smoke combustible tobacco cigarettes

Particulate matter

89. No available data.

Propylene glycol and glycerol

90. Propylene glycol is regarded as GRAS. Although data indicate that oral exposure to PG is not likely to cause adverse health effects, data from inhalation studies are limited. In some individuals, inhalation exposure to PG aerosols in concentrations found in E(N)NDS has been associated with eye and throat irritation.

91. Glycerol is also regarded as safe. Acute toxicity studies indicate the VG is less irritating to the upper respiratory airways than PG.

Nicotine

92. No available data.

Flavourings and their degradation products

93. While the Flavor and Extracts Manufacturers Association (FEMA) considers many flavours to be GRAS in food products, such chemicals could still be harmful when they are aerosolised and inhaled. Indeed, some are known have sensitising, toxic, or irritating potential. Although few studies have examined the effects of flavouring compounds following ingestion, some may have adverse health effects when inhaled.

94. The effects of several flavouring compounds were cited. Aldehydes were noted to cause irritation of the respiratory tract. Menthol causes cooling and local

anaesthesia, as well as having effects on drug absorption and metabolism, bronchodilation and respiration changes, and electrophysiology. Diacetyl, acetylpropionyl (2,3-pentanedione) and acetoin may cause adverse respiratory effects such as chronic cough and bronchitis, asthma, and bronchiolitis obliterans. Cinnamaldehyde, at low concentrations as found in E(N)NDS, is cytotoxic and genotoxic and adversely affects cell processes and survival and may impair homeostasis in the respiratory system. Benzaldehyde is associated with irritation of the eyes and mucous membranes of the respiratory tract during occupational exposure.

Other constituents and products formed on aerosolization

95. The authors noted that when evaluating the health effects of E(N)NDS, it is important to consider that e-liquids, when heated and aerosolised, may undergo chemical reactions that result in the formation of new compounds. For example, carbonyls such as formaldehyde, acetaldehyde, acrolein, and glyoxal are also generated from thermal decomposition of e-liquids. Formaldehyde is classified as a human carcinogen (Group 1) by IARC and acetaldehyde is possibly carcinogenic to humans (Group 2B). Glyoxal may cause mutagenicity and acrolein causes irritation of the nasal cavity and damages the lining of the lungs. Various parameters can affect the production of carbonyls, such as temperature, airflow, catalytic properties of metal heating coils, power of the coil and device design.

96. Overall, the report summarised that ‘when e-liquids are heated and aerosolised, they can produce chemical reactions that could form carbonyl compounds such as reactive aldehydes, which are considered to have toxic effects on human health. At temperatures within the range of most e-cigarette products (150°–350°C), formaldehyde, acetaldehyde, and acrolein have been detected at levels that have raised concerns about chronic health endpoints’.

97. TSNAs have also been reported in e-liquids and aerosols, probably from the pharmaceutical-grade nicotine used, which are known potent carcinogens.

98. A number of VOCs have been identified in e-liquids, including benzene (Group 1 carcinogen), toluene, ethylbenzene, m-xylene, p-xylene, o-xylene, styrene, ethyl acetate, ethanol, methanol, pyridine, acetylpyrazine and 2,3,5-trimethylpyrazine. In one study, the maximum concentrations of benzene, methanol, and ethanol detected in the samples were higher than their authorised maximum limits as residual solvents in pharmaceutical products (Lim and Shin, 2017 cited in NAS, 2018).

99. Thermal degradation of sweet e-liquids containing sugars was shown to produce furans such 5-hydroxymethylfurfural and furfural. Furfural is known to cause irritation to the upper respiratory tract in humans. Levels of furans in the E(N)NDS emissions were significantly correlated with power of the device and sweetener concentration, but not puff duration.

100. In one study, diethyl phthalate and diethylhexyl phthalate were found in e-liquids thought to have originated from the e-liquid packaging or during the e-liquid production process (Oh and Skin, 2015 cited in NAS, 2018). These antiandrogenic, estrogen-like compounds have been shown to initiate early breast development and IARC classified diethylhexyl phthalate as Group 2B (possibly carcinogenic to humans).

101. Regarding metals, a limited number of studies have detected metals in e-liquid and aerosols, including chromium, nickel, lead, manganese, aluminium, tin, and iron. The report noted that while it is well established that metals are highly toxic via inhalation, no studies have evaluated the specific health effects of metals in E(N)NDS, except in the study of copper nanoparticles from E(N)NDS and mitochondrial oxidative stress and DNA fragmentation.

102. Overall, authors concluded that 'several hazardous compounds have been found in liquids and in the heated aerosol produced by e-cigarettes, including formaldehyde, acetaldehyde, and acrolein, which are known carcinogenic toxicants. Of greater concern are the added flavorings that are considered safe for use in food, but have not been widely tested for sensitising, toxic, or irritating potency. E-cigarettes are also a source of extremely high particulate doses in the human respiratory system. Fine particles are emitted when humectants (mostly PG and glycerol) are aerosolised'.

US Department of Health and Human Services

103. Under the US Department of Health and Human Sciences, a report of the Surgeon General was published regarding E(N)NDS use among youth and young adults (U.S. Department of Health and Human Services, 2016). The report focused on short-term and potential long-term effects of use of E(N)NDS by youth and young adults and listed a number of conclusions outlined below.

Risk of E(N)NDS

104. Users of E(N)NDS are exposed to a variety of aerosolised chemicals, including solvents and flavouring chemicals added to e-liquids, as well as other toxins produced during the heating process. The health impacts of frequent exposure to such toxins in the aerosol are not well understood, although several are known carcinogens.

105. Research is needed to understand how different design features of E(N)NDS relate to potential toxicity. For example, if the compounds in e-liquids are affected by heating, changes in chemical composition, or pH; if these compounds are absorbed into the blood stream, and how additives in the e-liquid affect the availability of these compounds. Research is also needed to understand if potential health risks may be reduced by changes in product engineering.

106. Overall, the Surgeon General concluded that ‘E-cigarette aerosol is not harmless “water vapour” although it generally contains fewer toxicants than combustible tobacco products’.

107. In addition, ‘for e-cigarettes, biological data support a potential association with cardiovascular disease, and short-term use of these products is accompanied by a measurable increase in plasma nicotine concentrations in adults as well as increases in heart rate and blood pressure. Much more research is needed, but the limited data available suggest the typical cardiovascular effects exerted by nicotine are also exerted by e-cigarettes’’

Particulate matter

108. The report noted that E(N)NDS are a source of high doses of fine particles in the human respiratory system. Although mild respiratory effects have been documented adequate assessments are lacking.

109. Overall, results to date demonstrate that E(N)NDS produce submicron-sized particles and oxidising free radicals that may present a potential toxicological risk to E(N)NDS users.

Propylene glycol and glycerol

110. E(N)NDS produce PG aerosols at levels known to cause eye and respiratory irritation to both users and bystanders. However, only mild effects have been described in humans exposed to PG mist and little is known about long term effects. It was noted that inhaling PG can increase the risk of developing asthma.

111. Limited studies have examined the toxicity of PG and VG following chronic inhalation exposure. Animal studies have shown few toxicological effects following VG aerosol exposure except for mild squamous metaplasia in rats exposed to VG for 13 weeks. Inhalation studies with PG in rats and monkeys did not report treatment-related effects. However, no studies are available that investigated the potential inhalation toxicity of VG and PG in humans using E(N)NDS.

112. The report concluded that very little is known from human studies about the long term health effects of inhaling PG and VG from E(N)NDS aerosol although adverse effects have been detected in animal models. Further investigations are needed to improve the understandings of the effects of aerosolised VG and PG.

Nicotine

113. Animal research indicates adolescent brains are particularly sensitive to the effects of nicotine and this age group is at risk for nicotine-induced neural and behavioural alterations. Based on existing evidence from both human and animal studies, which show detrimental effects of nicotine on adolescent brain development, the use of E(N)NDS in adolescents should be avoided and actively discouraged. However, further research is needed to more fully understand the effects of E(N)NDS use in adolescents.

114. The authors cited the 2014 Surgeon General's report that stated that smoking increases the risk for disease via a number of biological pathways which are activated by nicotine; nicotine exposure during foetal development has lasting adverse consequences for brain development; nicotine adversely affects maternal and foetal health during pregnancy which may contribute to multiple adverse outcomes such as preterm delivery and stillbirth; and nicotine exposure during adolescence which is a critical window for brain development, may have long lasting adverse consequences for brain development and cognition. The report stated that 'pregnant women and women intending to become pregnant should be cautioned against using e-cigarettes to avoid unnecessary nicotine exposure to their baby'.

115. The report concluded that 'nicotine exposure during adolescence can cause addiction and can harm the developing adolescent brain'. Moreover, 'nicotine can cross the placenta and is known to affect foetal and post-natal development. Therefore, nicotine delivered by e-cigarettes during pregnancy can result in multiple adverse consequences including sudden infant death syndrome, and could result in altered corpus callosum, deficits in auditory processing and obesity'.

Flavourings and their degradation products

116. The Surgeon General's report noted that little is known about flavouring chemicals used in e-liquids and more than 7700 unique flavours are available. Many of such chemicals are considered GRAS for ingestion. However, they have not been adequately tested when heated at temperatures when inhaled in an aerosolised form. The FEMA in the US reported, in an official statement, that 'ingredients in flavours are evaluated for exposure through ingestion only; thus, any results cannot be extrapolated to use through inhalation'.

117. A number of studies have shown that flavouring compounds exert adverse health effects when inhaled. *In vitro* cytotoxicity assays showed flavourings were cytotoxic in human embryonic and mouse neuronal stem cells but not human pulmonary cells. In one study (Farsolinos et al., 2014 cited in U.S. Department of Health and Human Services, 2016), diacetyl (2,3-butanedione) was detected in the majority of e-liquids tested, which is associated with decreased lung function and the development of bronchiolitis obliterans.

118. The report concluded by noting that the health effects and potentially harmful doses of heated and aerosolised constituents of e-liquids such as flavouring compounds are not completely understood as they have not been fully investigated for their potential sensitising, irritant or toxic effects when inhaled.

Other constituents and products formed on aerosolization

119. Users of E(N)NDS are exposed to several chemicals including nicotine, carbonyl compounds, TSNAs and VOCs, all of which are known to cause adverse health effects. TSNAs including NNN and NNK are classified as Group 1 carcinogens by IARC. They are present in e-liquids due to extraction process used to extract nicotine from tobacco leaves or the addition of tobacco flavourings.

Nitrosation reactions can occur in e-liquids, especially during inadequate storage or manufacturing processes, which is thought to increase the levels of NNN.

120. Carbonyls such as formaldehyde, acetaldehyde, and acrolein are present in E(N)NDS and long-term exposure can increase the risk of cancer. Formaldehyde has been classified as carcinogenic to humans by the US Environmental Protection Agency; acrolein can cause ocular and respiratory irritation and is a probable carcinogen and has been linked to several pulmonary diseases such as lung cancer, asthma and COPD, as well as cardiovascular disease. The authors noted that although amounts of formaldehyde and acetaldehyde detected in e-liquids are relatively low compared to CCs, they should be controlled to the lowest possible concentrations as they may be formed when e-liquids are heated. In addition, users will be exposed to high concentrations of carbonyls as larger capacity batteries and heating mechanisms are developed.

121. Heavy metals, such as lead and cadmium, have also been found in E(N)NDS aerosols and e-liquids, many of which have been linked with respiratory disease. Authors noted that metals are produced by the aerosolisation of e-liquids and by flaws in e- cigarette heating mechanisms and poor quality control.

122. Overall, it was concluded that although typical constituents of E(N)NDS aerosol have been identified, the potential short- and long-term health effects following inhalation of the heated and aerosolised constituents of the e-liquid require further investigation. However, there is a limitation to understanding the health impact of chemical reactions due to the heterogeneity of E(N)NDS devices (voltage), e-liquids (quality, ingredients), and use behaviours (puff duration), as emissions may be altered by any combination of these mechanical and behavioural differences.

Bystander exposure

123. A number of studies have been conducted to investigate potential health effects of second-hand exposure to E(N)NDS aerosol. Although no changes in lung function were reported, exposure to E(N)NDS in bystanders caused an increase in serum cotinine similar to that seen from passive exposure to CC smoke. This indicates the need to investigate the impact of passive aerosolised nicotine inhalation on long-term lung function in bystanders.

124. Other studies investigated the health risks of passive exposure to E(N)NDS. Offerman, 2015 (cited in U.S. Department of Health and Human Services, 2016) noted that in bystanders, nicotine and PG exceeded California EPA exposure level standards for non-carcinogenic health effects following indirect exposure. In contrast, when compared to workplace exposure standards, Burstyn compared E(N)NDS aerosol exposure to workplace exposure standards and concluded that none of the constituents in E(N)NDS aerosol were of health concern in bystanders (Burstyn, 2014 cited in U.S. Department of Health and Human Services, 2016). Authors noted that workplace exposure is not appropriate to apply to the population as a whole, and exposure scenarios in the workplace and via E(N)NDS use are different.

125. The report suggested the potential for allergic reactions in bystanders should also be considered. For example, dermal and oral exposure to PG is known to cause dermatitis and allergic sensitisation. As several e-liquids contain flavourings derived from nuts, research should be carried out to investigate whether bystanders can have allergic reactions from allergens in E(N)NDS aerosol.

New Zealand

Ministry of Health

126. The Ministry of Health in New Zealand published a document providing information on E(N)NDS aimed at healthcare professionals. This publication covered health risks of nicotine, E(N)NDS, E(N)NDS vapour and second-hand vapour (New Zealand Ministry of Health, 2016). The main points and conclusions are summarised below.

Risk of E(N)NDS

127. Regarding potential health risks, the Ministry of Health stated that short-term use of E(N)NDS may cause headaches, dry mouth or throat, and throat or mouth irritation but the risks following long-term use are unknown. However, the risks from smoking are likely to be much greater, and there is evidence that E(N)NDS pose fewer health risks to smokers who switch completely from tobacco smoking to E(N)NDS.

128. A number of chemicals have been found in E(N)NDS aerosol. However, under typical usage conditions such chemicals are present at very low levels, which are many times lower than found in tobacco smoke.

129. The Technical Expert Advisory Group: Electronic Cigarette Product Safety minutes from a meeting in October 2017 noted that a suggestion was made that independent toxicology reports are required.

Propylene glycol and glycerol

130. The Technical Expert Advisory Group: Electronic Cigarette Product Safety minutes from a meeting in March 2018 noted a discussion on the current evidence around the toxicity of PG and VG in e-liquid. The minutes noted that the Ministry will investigate further and will return to this topic in a future meeting but, currently, there is no evidence of any safety concerns with the vaping liquid being 100% PG or VG.

Nicotine

131. The Ministry of Health stated that ‘the nicotine found in tobacco does not cause the negative health effects associated with smoking. It is the other chemicals found in tobacco smoke that are harmful. However, nicotine is an addictive chemical that encourages smoking. For smokers, the nicotine in e-cigarettes poses little danger, however, in excessive amounts, it can be lethal, especially for children. In

order to prevent accidental poisoning, especially of children, e-cigarettes and e-liquids should be stored where they cannot be accessed by others'.

132. The Technical Expert Advisory Group: Electronic Cigarette Product Safety minutes from a meeting in March 2018 noted a discussion on the current evidence around nicotine and its toxicity. There was agreement that the toxic level of nicotine is unknown. There was also discussion on the maximum allowable nicotine strength in other jurisdictions, including the Tobacco Products Directive.

Bystander exposure

133. It was concluded that 'the risks from second-hand vapour are unknown at this stage. However, second-hand vapour is known to be less harmful than second-hand smoke'.

Australia

National Health and Medical Research Council

134. In 2017, the NHMRC of the Australian Government issued a high-level statement that covered potential health risks of E(N)NDS. The main points and conclusions are summarised below (NHMRC, 2017).

Risk of E(N)NDS

135. NHMRC stated that it is believed that E(N)NDS are less harmful than tobacco cigarettes as they expose users to few toxic chemicals, although there is insufficient evidence to quantify the reduction in risk compared to CCs. A 2014 study was cited that reported that E(N)NDS are 95% less harmful that tobacco products, although it was caveated that this finding was based on opinion rather than empirical evidence.

Particulate matter

136. NHMRC reported various studies that demonstrated that users of E(N)NDS and bystanders were exposed to PM. Such particulates may worsen existing illnesses or increase the risk of developing diseases such as cardiovascular or respiratory disease. Authors cited a WHO report[6] that stated that exposure to any level of PM may be harmful and that levels of exposure should be minimised.

Propylene glycol and glycerol

137. Regarding e-liquids, NHMRC cited that E(N)NDS are not risk free and may expose users to chemicals at levels that have the potential to cause health effects, including PG, VG or ethylene glycol, which may form toxic or carcinogenic compounds when vaporised. Although many of these chemicals are typically found in lower concentrations compared with CCs, in some studies E(N)NDS and CCs were found to produce similar levels of some chemicals i.e. formaldehyde. E-liquids

6 WHO, 2006. WHO air quality guidelines for particulate matter, ozone, nitrogen dioxide ad sulfur dioxide: summary of risk assessment. WHO, Geneva.

or aerosol may also contain potentially harmful chemicals which are not present in CC smoke.

Flavourings and their degradation products

138. With regard to flavouring compounds, NHMRC considered that while some of the chemicals in e-liquids are used in food production and are generally considered safe when ingested, little was known regarding their safety when inhaled as an aerosol directly into the lungs. A number of studies were cited that reported harmful effects when food-approved flavourings are inhaled, including cherry, cinnamon and popcorn flavours. Overall, there is a growing body of evidence to suggest that the long-term inhalation of flavourings used in e-liquids is likely to pose a risk to health.

Other constituents and products formed on aerosolization

139. NHMRC stated that E(N)NDS may expose users to metals such as aluminium, arsenic, chromium, copper, lead, nickel and tin as they have been detected in e-liquid and the aerosol produced during use. These metals have been detected at levels greater than, or similar to, those found in CCs.

National Industrial Chemicals Notification and Assessment Scheme

140. The NICNAS summarised potential human health effects related to E(N)NDS use (NICNAS, 2019).

Risk of E(N)NDS

141. In the summary and key findings, NICNAS stated that ‘E-cigarette use can cause acute adverse health effects (to which nicotine may be a contributing factor), although the chronic effects of e-cigarette use on health are unknown’.

Particulate matter

142. Second-hand emissions can be inhaled by the user or bystanders, which is known as passive vaping. Authors noted several reports in the scientific literature describing PM in first- and second-hand emissions. Due to their small size, PM can stay suspended in air for long periods of time. When inhaled, the size of the particle determines the site of deposition in the lungs, with smaller particles being likely to deposit deeper within the respiratory tract. The particulate characteristics of E(N)NDS emissions and modelling of their lung distribution indicate there is significant deposition in the alveoli.

143. Overall, authors concluded that ‘the persistence of chemicals in second-hand E(N)NDS emissions as suspended PM and in the gaseous phase may result in additional chemical exposure through passive inhalation. Once the particles settle, there is also the potential for dermal exposure’.

Nicotine

144. Health effects following exposure to nicotine through E(N)NDS use was outside the scope of the NICNAS report. However, authors did note that E(N)NDS use can cause acute adverse health effects, to which nicotine may be a contributing factor, although the chronic effects of E(N)NDS use on health are unknown.

Flavourings and their degradation products

145. NICNAS identified over 200 flavouring compounds in the scientific literature that are added to e-liquids, some of which have been cited in scientific literature as causing health concerns following E(N)NDS use. Authors noted that diketone flavourings are associated with permanent lung damage, also known as popcorn lung. Other health concerns include respiratory irritation, sensitisation, acute toxicity, impaired cell function, and the potential to form harmful reaction products. However, the actual risk to human health posed by flavouring compounds is yet to be determined. Flavouring compounds, either alone, or as mixtures in e-liquids, or from E(N)NDS emissions without nicotine, are also described as having adverse effects on the viability and function of various *in vitro* cell culture models.

146. It was also reported that flavouring chemicals can form reaction products with PG during storage, and the chemical species produced may be harmful to human health.

147. Overall, authors stated that further research is required to establish the safety of flavouring chemicals for use in e-liquids as exposure to these chemicals occurs through the inhalation route and there is a potential for the formation of reaction products during heating.

Other constituents and products formed on aerosolization

148. E(N)NDS emissions contain carbonyl reaction products, including acetaldehyde, acetone, acrolein and formaldehyde, which may pose a risk to human health. Formaldehyde is the most frequently measured reaction product and is usually present at the highest concentration compared with other reaction products, although actual measured levels vary widely between different research groups. Authors also noted that it is uncertain whether carbonyls produced during typical E(N)NDS use are accurately reflected in laboratory studies. Therefore, authors concluded that the relevance of observed amounts of carbonyl compounds generated from E(N)NDS devices to human health is uncertain. There is, however, conclusive evidence that E(N)NDS generate carbonyl compounds.

149. E(N)NDS emissions also contain contaminants that are derived from the E(N)NDS device, including metals (arsenic, chromium, lead, mercury and nickel), VOCs, phthalates, pesticides and TSNAs, which at a sufficient concentration and exposure, may have the potential to pose a risk to human health.

Australian Commonwealth Department of Industry, Innovation and Science

150. In 2018, Byrne et al. carried out a literature search on behalf of the Department of Industry, Innovation and Science for papers published between January 2017 and March 2018 (Byrne et al., 2018). Search terms included e-cigarettes, electronic cigarettes, ENDS, electronic nicotine delivery system, vape and vaping. A number of topics were included in the review including the health risks of E(N)NDS in human, animal and *in vitro* studies (Byrne et al., 2018). The main points and conclusions are summarised below.

Risk of E(N)NDS

151. Authors stated a number of conclusions and key findings. Based on human studies, authors concluded that large cross-sectional studies showing a link between asthma and E(N)NDS use in adolescents may present temporal ordering i.e. asthma prompts a switch to E(N)NDS. Regarding cardiovascular disease, the paucity of long terms studies means that there is no evidence that E(N)NDS use is associated with clinical cardiovascular disease. Although carcinogenic compounds and metabolites from E(N)NDS are present in users, the risk of developing cancer or other health effects is unclear. E(N)NDS use may impair lung function although due to confounding by CC smoking, the effects of E(N)NDS alone are unclear.

152. Animal data were also assessed. Authors concluded that E(N)NDS aerosol can cause significant damage to rats and mice, as increased release of pro-inflammatory cytokines, emphysematous lung destruction, renal, hepatic and heart fibrosis were observed in rodents exposed to E(N)NDS aerosols or intravenous e-liquids. Significant effects on offspring of exposed pregnant mice and frog embryos were also seen, including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects.

153. A number of other topic areas not covered by previous reviews were identified, including wound healing following surgery, exposure to carcinogens and flame retardants from E(N)NDS, a relationship between E(N)NDS use and oral mucosal lesions, allergic reaction following exposure to mercaptobenzothiazole and oxidative stress in E(N)NDS users following chronic use.

154. Overall it was concluded ‘that the evidence available suggests that regular use of e-cigarettes is likely to have adverse health consequences. There is a lack of clarity about the magnitude of adverse health effects and the quantity of e- cigarette use required to trigger adverse health effects’.

Propylene glycol and glycerol

155. Authors noted that the toxicity of E(N)NDS is likely to be associated with thermal decomposition by-products from e-liquid constituents such as PG and VG.

Nicotine

156. Based on new studies identified in the review, authors noted that the most robust study attributed increased cardiac sympathetic nerve activity to the use of E(N)NDS containing nicotine. There was also an association between nicotine and increased heart rate and blood pressure, although one study reported an increase in diastolic blood pressure after nicotine intake from E(N)NDS whereas other studies reported increased systolic blood pressure.

157. Nicotine may also have anti-inflammatory effects and affect wound healing due to the vasoconstrictive effects. Authors also suggested that 'short term e-cigarette exposure does not lead to changes in oxidative stress although it may be associated with habitual e-cigarette use'.

Flavourings and their degradation products

158. It was noted that the toxicological response to E(N)NDS aerosol is dependent on its constituents as different brands and flavours contain different chemicals. A number of flavouring compounds were shown to be cytotoxic or reduce cell viability in lung cells. Some flavourings induced low levels of hydrogen peroxide in human pleural tissue indicating low levels of oxidative stress. However, mixing flavourings together led to increased reactive oxygen species production. Flavouring compounds have also been shown to increase pro-inflammatory cytokines, phagocytosis, neutrophil extracellular traps formation and natural killer cells. Overall, it was concluded that flavourings can have different effects on inflammatory responses.

Japan

159. The Ministry of Health, Labor and Welfare does not appear to have any documents related to toxicological effects of E(N)NDS published in English.

Selected Societies and Expert Groups

Forum of International Respiratory Societies

160. In 2014, the Forum of International Respiratory Societies published their first position statement regarding E(N)NDS. A later position statement was published in 2018 that addresses risks of E(N)NDS use, particularly in adolescents and young adults (Ferkol et al., 2018). The main points and conclusions are summarised below.

Risk of E(N)NDS

161. The position statement noted that although the NAS found evidence that exposure of potentially harmful chemicals from E(N)NDS is significantly lower than CC, this does not mean that E(N)NDS aerosols are "harmless vapour", as they contain particulates, VOC and heavy metals, such as nickel, tin and lead.

162. It was noted that exposure to aerosol extracts causes DNA damage in human oral and lung cells, and inhalation of aerosols may lead to pulmonary inflammation,

impaired innate immunity, reduced lung function and changes consistent with chronic obstructive lung disease (emphysema) in animal models. This highlights the need to investigate the long-term risks.

163. Studies in humans, including adolescents have reported chronic or recurrent respiratory symptoms following E(N)NDS use. The authors concluded that 'these findings suggest that inhalation of vapour is not innocuous and raises concern that electronic cigarettes should not be prescribed as a safe or harmless tobacco alternative'.

164. Overall, regardless whether nicotine is present or not, exposure to E(N)NDS aerosol in adolescence and early adulthood is not risk-free and can result in pulmonary toxicity. More research is needed to understand the physiological and deleterious effects of electronic cigarettes.

Particulate matter

165. The concentration of ultrafine particles, size distribution and deposition pattern in the lungs is similar for E(N)NDS aerosol and CC.

Flavourings and their degradation products

166. It was stated that flavouring compounds that have been shown to be safe when ingested may be toxic when inhaled. These substances are not inert and have been shown to injure airway epithelial cells *in vitro*.

Tobacco Advisory Group of the Royal College of Physicians

167. The Tobacco Advisory Group of the Royal College of Physicians (RCP) published the report to provide an update on the use of harm reduction in tobacco smoking from all non-tobacco nicotine products, including E(N)NDS (RCP, 2016). The main points and conclusions are summarised below.

Risk of E(N)NDS

168. The report stated that 'there is very little evidence that short-term use of e-cigarettes causes any appreciable harm to users or to others, but information on long-term health effects of repeated and sustained inhalation of e-cigarette vapour is of necessity limited to inference, based on knowledge of the vapour's constituents'.

169. It was noted that particulates, carcinogens and other toxins would be expected to increase the risk of diseases that are usually associated with smoking CC such as lung cancer, COPD, cardiovascular disease and other diseases. However, the level of risk is expected to be lower compared with CC.

170. E(N)NDS are generally well tolerated with short-term adverse health effects relating mainly to mouth and throat irritation.

171. Due to limited data on potential long-term adverse effects of E(N)NDS, the predicted risks are based on long-term inhalation of known constituents of E(N)NDS

aerosol, including VOCs, carbonyls, aldehydes, TSNAs and metal particles. All occur at much lower levels than in CC smoke.

172. The deposition, absorption and excretion of TSNAs and other carcinogens in CC smoke may account for the increased risks of cancer of the oropharynx, stomach, bladder and other organs involved in the absorption and excretion process in smokers. It was noted that the presence of carcinogens in E(N)NDS aerosol may increase the risk of such cancers but the magnitude of any increase in risk, in either relative or absolute terms, is likely to be low due to the very low levels of exposure generated by E(N)NDS aerosol.

173. Overall, it was concluded that 'some of the carcinogens, oxidants and other toxins present in tobacco smoke have also been detected in e-cigarette vapour, raising the possibility that long-term use of e-cigarettes may increase the risks of lung cancer, COPD, cardiovascular and other smoking-related diseases. However, the magnitude of such risks is likely to be substantially lower than those of smoking, and extremely low in absolute terms. These potential health risks arise primarily from contaminants and components generated by the vaporisation process, which should be amenable to reduction through technological and purity improvements. Although it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products and may well be substantially lower than this figure'.

Particulate matter

174. Authors concluded that 'although e-cigarette vapour contains fewer toxins compared with CC, and those present are typically at much lower levels, it is appropriate to consider potential hazards of e-cigarettes in relation to this spectrum of harm'.

Propylene glycol and glycerol

175. Acute exposure to PG may cause airway irritation and cough in humans, and minor airflow obstruction. Studies of repeated inhalation in rats with PG or VG found no evidence of lung toxicity.

Nicotine

176. The report suggested that the long-term effects of nicotine are likely to be minimal, although chronic inhalation effects of nicotine have not been studied. Moreover, it was stated that there are no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption.

177. Research from animal studies suggests that nicotine exposure during both the foetal and the adolescent periods can adversely affect cognitive function and development. The relevance of these findings to human brain development remains uncertain.

Flavourings and their degradation products

178. Although the flavours used in the e-liquids are generally considered safe when ingested, some are irritant to the airways. The safety of most flavouring compounds after heating and inhalation is unknown.

179. Aerosol produced from e-liquids containing flavours has been demonstrated to be more cytotoxic than unflavoured aerosol and may increase airway inflammation.

180. Overall, it was concluded that 'although no study so far shows any clear hazards of flavours in e-cigarette vapour, those derived from flavours seem the most likely to pose appreciable health risks from long-term use'.

Other constituents and products formed on aerosolization

181. Levels of formaldehyde and other aldehydes can be relatively high when vaporisation occurs at high temperatures. However, such overheating generates an aversive taste known as a 'dry puff'.

182. Although the presence of toxins per se during normal use of E(N)NDS is of concern, the low levels measured indicate their presence is of lower concern. It was noted that under typical use conditions, toxin levels in inhaled E(N)NDS aerosol are probably well below prescribed threshold limit values for occupational exposure, indicating significant long-term harm is unlikely. Moreover, the magnitude of any risks relative to risk from CC smoking is likely to be small. However, consideration of the potential harm of long-term E(N)NDS use should serve as a guide to evidence-based product development, regulation and monitoring.

Bystander exposure

183. E(N)NDS users exhale aerosol, which may be inhaled by bystanders, leading to passive exposure to nicotine. There is, however, no direct evidence that such passive exposure is likely to cause significant harm. Nicotine from exhaled aerosol can be deposited on surfaces, but at such low levels that there is no plausible mechanism by which such deposits could enter the body at doses that would cause physical harm.

184. The report concluded that harm to others from aerosol exposure is negligible.

Royal College of General Practitioners

185. The Royal College of General Practitioners (RCGP) issued a position statement on the use of electronic nicotine aerosol products (E(N)NDS) in 2017 (RCGP, 2017). The report covered the toxicity of E(N)NDS as well as concerns, questions and recommendations.

Risk of E(N)NDS

186. The report cited that CC smokers are exposed to over 5000 chemicals, many of which are toxic or carcinogenic. However, E(N)NDS have significantly lower levels of key toxicants compared to CC, with average levels of exposure falling well below the thresholds for concern.

187. Concern was noted that there are little data available on the long-term effects of E(N)NDS and therefore the long-term safety profile of E(N)NDS use is still to be evaluated.

188. The report cites that 'it is accepted that based on the evidence to date, vaping is a far safer alternative to smoking tobacco. Public Health England and the Royal College of Physicians estimate that e-cigarettes are unlikely to exceed 5% of the harm from conventional smoking'.

Bystander exposure

189. The report concludes that 'there is no good evidence to suggest that passively breathing vapour from e-cigarettes is likely to be harmful'.

European Respiratory Society

190. The European Respiratory Society (ERS) established a task force to collect, analyse and integrate current knowledge on E(N)NDS and to provide an evaluation for various stakeholders, including physicians, scientists, patients, users and policymakers. In 2019, a task force report was published outlining their findings (Bals et al., 2019) . The main points and conclusions are summarised below.

Risk of E(N)NDS

191. In the conclusion the report, it was noted that E(N)NDS aerosol contains a number of potentially toxic chemicals but the composition and probably the toxicity varies across devices and liquids.

192. Experimental human studies demonstrate acute cardiovascular effects in E(N)NDS users that are consistent with stimulant effects of nicotine, but there is a lack of studies evaluating the long-term effects of E(N)NDS.

193. It was suggested that evidence that E(N)NDS cause disease in users is lacking as products have not been used long enough to observe possible chronic disease associations. However, as most users are former and current CC smokers, causation is difficult to establish. Compared to CC, fewer chemicals are found in E(N)NDS aerosol and generally at much lower concentrations.

194. Overall, authors noted that 'at the present time it cannot be concluded that long-term use of e-cigarettes is safer than that of tobacco product'.

195. The conclusions made by the ERS are in line with the FIRS position statement on E(N)NDS that stated that 'health risks of electronic cigarettes have not

been adequately studied' and thus 'potential benefits to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine'. The task force suggested cautious use and application of e-cigarettes to avoid potential health effects.

Particulate matter

196. Exposure to particulates from CC cigarettes and air pollution is associated with irritant and oxidant effects and increased incidence of cardiovascular disease. However, the composition of particles from the combustion of organic materials are much more complex and include solid carbonaceous materials compared with particulates in E(N)NDS aerosol. However, nanoparticles in aerosol are of concern because they are more persistent, and some nanoparticles are known to cross capillaries in the lung and enter the systemic circulation. To date, the hazards posed by nanoparticles generated by E(N)NDS are unknown.

Propylene glycol and glycerol

197. Animal studies investigating the inhalational toxicity of PG have reported few adverse effects. However, temperature-dependent thermal degradation of PG and VG results in the formation of potentially toxic aldehydes including acetaldehyde, formaldehyde and acrolein. These can be irritant, carcinogenic, and can contribute to cardiovascular and pulmonary toxicity. However, concentrations of these aldehydes in E(N)NDS aerosol are much lower compared with CC smoke although high concentrations can occur under conditions of high heating coil temperature devices or during "dry puffing".

Nicotine

198. Nicotine present in E(N)NDS is thought to contribute to their toxic effects.

Flavourings and their degradation products

199. The report noted that several flavouring chemicals are of toxicological concern. Benzaldehyde and cinnamaldehyde are irritants and cytotoxic and are of concern in terms of chronic respiratory effects; diacetyl, acetyl propionyl and acetoin are associated with pulmonary inflammation including bronchiolitis obliterans. It was noted that diacetyl has been approved for ingestion but has caused adverse health effects when inhaled. This is of concern as it was found to be present in a many sweet-flavoured e-liquids, albeit at lower levels compared with CC smoke.

200. There is evidence that some flavouring chemicals undergo thermal degradation, forming other toxic chemicals.

201. It was concluded that due to the large number of flavours available, a detailed toxicological evaluation of each component has not been carried out, therefore the health effects of many flavouring compounds are largely unknown.

Other constituents and products formed on aerosolization

202. High concentrations of metals, including cadmium, nickel and chromium are released from heating coils, which are carcinogenic and can cause cardiovascular and/or pulmonary disease. However, levels of metals in E(N)NDS aerosols are typically lower than those from CC.

Bystander exposure

203. The potential of harm to bystanders following exposure to second-hand E(N)NDS aerosols is currently unknown. Potential health risks are dependent on the individual exposure conditions, such as the composition of the e-liquids used, the vaping topography of the users, the number of users, the dimensions of the room, the amount of ventilation, and the duration of exposure. There are a limited number of studies on second-hand exposures to E(N)NDS, and they do not provide sufficient evidence enough to exclude a potential risk.

204. Overall, it was concluded that 'while it is highly likely that involuntary indoor exposure to e-cigarette chemicals is much less hazardous than exposure to second-hand cigarette smoke, it is possible that such exposure could present a potential health risk, especially to vulnerable populations, including children, pregnant women and people with cardiovascular or respiratory impairments. More research is needed in order to allow for a solid risk assessment'.

Summary

Risk of E(N)NDS

205. Short-term use of E(N)NDS may cause headaches, dry mouth or throat, and throat or mouth irritation. Little data are available regarding the long-term use. However, most authoritative bodies noted that E(N)NDS are unlikely to be harmless, and long-term use may increase the risk of COPD, lung cancer and potentially cardiovascular disease (Ferkol et al., 2018; Grana et al., 2013; NAS, 2018; RCGP, 2017; U.S. Department of Health and Human Services, 2016; WHO, 2016). The comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be lower than the risks of smoking CCs (McNeill et al., 2018). For ex-smokers and never smokers, use of E(N)NDS will increase the risk of harm to health. It was also widely noted that existing evidence also shows that E(N)NDS aerosol may pose a risk to adolescents and fetuses (Byrne et al., 2018; Ferkol et al., 2018; McNeill et al., 2018; NAS, 2018; Pisinger, 2015; RCGP, 2017; U.S. Department of Health and Human Services, 2016; WHO, 2014, 2016).

Particulate matter

206. A number of authoritative bodies noted that particle size distribution and the number of particles delivered by E(N)NDS is similar to that of CCs with most being in the ultrafine range (<1 µm). Although mild respiratory effects have been documented adequate assessments are lacking and the hazards posed by such particles generated by E(N)NDS are unknown. However, they may present a potential

toxicological risk to E(N)NDS users (Grana et al., 2013; NICNAS, 2019; U.S. Department of Health and Human Services, 2016; WHO, 2014).

Propylene glycol and glycerol

207. Short-term effects of E(N)NDS include eye and respiratory irritation caused by exposure to PG. Acute toxicity studies indicate the VG is less irritating to the upper respiratory airways than PG. PG may increase the risk of developing asthma.

208. PG and VG are both considered to be GRAS following ingestion. Limited studies have investigated the toxicity of PG and VG following chronic inhalation. Some authoritative bodies concluded that PG and VG may be of potential concern due to effects irritation seen in animals and humans (BfR, 2012a; Byrne et al., 2018; Grana et al., 2013; NAS, 2018; Pisinger, 2015; U.S. Department of Health and Human Services, 2016; WHO, 2014) although little is known about the long term effects of chronic exposure. In contrast, the New Zealand Ministry of Health Technical Expert Advisory Group: Electronic Cigarette Product Safety stated that there is no evidence of any safety concerns with the e-liquids being 100% PG or VG.

209. Many authoritative bodies noted the thermal degradation products may contribute to the toxicity of E(N)NDS (Byrne et al., 2018; Grana et al., 2013; McNeill et al., 2018; NHMRC, 2017). These include aldehydes acetaldehyde (Group 2B carcinogen), formaldehyde (Group 1 carcinogen), propylene oxide (Group 2B carcinogen) and acrolein, which can cause upper respiratory tract irritation and can contribute to cardiovascular and pulmonary toxicity.

Nicotine

210. Most authoritative bodies agreed that both human and animal data indicate adverse health effects may occur following foetal exposure during periods of developmental vulnerability and adolescent exposure. These include impaired foetal brain and lung development, sudden infant death syndrome, altered corpus callosum, deficits in auditory processing and obesity, and altered brain development in adolescents, which may potentially lead to learning and anxiety disorders (Pisinger, 2015; RCP, 2016; U.S. Department of Health and Human Services, 2016; WHO, 2016).

211. Overall, several reports suggest that the evidence is sufficient to caution children and adolescents, pregnant women and women of reproductive age about ENDS use because of the potential for foetal and adolescent nicotine exposure to have long term consequences for brain development (U.S. Department of Health and Human Services, 2016; WHO, 2014, 2016).

212. In contrast, PHE noted that while nicotine could theoretically cause adverse health effects, long-term use of nicotine by snus users, at systemic concentrations seen in CC smokers and E(N)NDS users, has not caused serious health effects in adults, and use of nicotine replacement therapy by pregnant smokers has not increased risks to the fetus (McNeill et al., 2018). The Tobacco Advisory Group of

the RCP suggested that the long-term effects of nicotine are likely to be minimal, although chronic inhalation effects have not been studied. Moreover, it was stated that there are no grounds to suspect that inhaled nicotine will have an appreciably different risk profile from nicotine delivered via other routes of absorption (RCP, 2016).

213. Based on new study data, a number of authoritative bodes identified an association of nicotine and cardiovascular disease, increased heart rate and blood pressure (BfR, 2012b; Byrne et al., 2018; Pisinger, 2015; WHO, 2016).

Flavourings and their degradation products

214. All authoritative bodies agreed that most flavouring compounds are GRAS when ingested, but such chemicals could be harmful when heated, aerosolised and inhaled. In addition, it was noted that few data are available about potential health effects of flavouring compounds following inhalation but some are known to have sensitising, toxic, or irritating potential and may pose appreciable health risks from long-term use (Bals et al., 2019; Ferkol et al., 2018; NAS, 2018; NHMRC, 2017; NICNAS, 2019; Pisinger, 2015; RCP, 2016; U.S. Department of Health and Human Services, 2016; WHO, 2016).

215. NICNAS noted that some flavouring chemicals can also form reaction products with PG during storage, and form degradation products on heating, both of which may be harmful to human health (NICNAS, 2019).

Other constituents and products formed on aerosolization

216. When evaluating the health effects of E(N)NDS, it is important to consider that e-liquids, when heated and aerosolised, may undergo chemical reactions that result in the formation of new compounds. Many authoritative bodies reported that carbonyls, VOCs, TSNAs have all been detected in E(N)NDS aerosol, the levels of which, apart from formaldehyde, are generally lower in E(N(NDS aerosol than in CC smoke (Grana et al., 2013; U.S. Department of Health and Human Services, 2016; Visser et al., 2015; WHO, 2016). However, many of the degradation products are irritant, toxic, mutagenic or carcinogenic.

217. Many authoritative bodies noted the presence of metals in E(N)NDS aerosols, most reporting that concentrations are equal or greater than CCs or at sufficient concentration that may pose a risk to health (NHMRC, 2017; NICNAS, 2019; WHO, 2016).

218. In contrast, RIVM and ERS noted levels were lower than CC and PHE noted that levels in aerosol do not give rise to significant health concerns (Bals et al., 2019; McNeill et al., 2018; Visser et al., 2015).

Bystander exposure

219. Conflicting opinions were reported regarding risk to bystanders from E(N)NDS exposure. A number of authoritative bodies concluded that although many

chemicals, metals, nicotine, and PM emitted from E(N)NDS were lower compared to CC, the risk that passive exposure to E(N)NDS vapour in bystanders could lead to adverse health effects, such as short-term lung obstruction and eye and respiratory tract irritation cannot be excluded. The magnitude of risk is unknown (Bals et al., 2019; Pisinger, 2015; WHO, 2016).

220. In contrast, PHE concluded that there have been no identified health risks in bystanders and the Tobacco Advisory Group of the RCP concluded that harm to bystanders from exposure to E(N)NDS aerosol is negligible (McNeill et al., 2018; RCP, 2016).

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Abbreviations/Glossary

ANSES	Agency for Food, Environmental and Occupational Health & Safety
BfR	Federal Institute for Risk Assessment
BMDL	Lower 95% confidence interval of the benchmark dose
CC	Conventional Cigarettes
COP	Conference of the Parties
COPD	Chronic obstructive pulmonary disease
E(N)NDS	Electronic Nicotine and Non-Nicotine Delivery Systems
ENDS	Electronic Nicotine Delivery Systems
ENNDS	Electronic Non-Nicotine Delivery Systems
ERs	European Respiratory Society
FEMA	Flavour Extracts Manufacturers Association
IARC	International Agency for the Research on Cancer
LED	Light-Emitting Diode
MOE	Margin of exposure
NAS	US National Academies of Sciences, Engineering and Medicine
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N′-nitrosonornicotine
NOAEC	No observed adverse effect level
NOAEL	No observed adverse effect level
PAH	Polycyclic Aromatic Hydrocarbon
PG	Propylene Glycol
PHE	Public Health England
RCGP	Royal College of General Practitioners
RCP	Royal College of Physicians
RIVM	National Institute for Public Health and the Environment
TSNA	Tobacco-Specific Nitrosamine
VG	Vegetable glycerol
VOC	Volatile Organic Compound
WHO	World Health Organization

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