Principles that Underpin the Current Policy and Regulatory Approach to Electronic Cigarettes (E-Cigarettes) in Australia

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Latest Evidence

- In August 2016, a World Health Organization (WHO) report concluded that the evidence for the safety of e-cigarettes[1] and their capacity to aid smoking cessation has not been established, and that there are possible risks from active and passive exposure to electronic cigarette vapour. The WHO raises additional concerns about the risk that e-cigarettes may serve to initiate young people into nicotine use and smoking.
- The WHO highlights a range of scientific uncertainties in relation to e-cigarettes, including that simple comparisons of toxicant levels in e-cigarette aerosol to the high levels in tobacco smoke, as advocated by the tobacco industry, 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 tobacco smoking.
- A 2016 US Surgeon General's report stated that exposure to nicotine in adolescents via e-cigarettes may have long-term consequences for brain development, potentially leading to learning and mood disorders. The report also stated that 'the use of products containing nicotine poses dangers to youth, pregnant women, and fetuses. The use of products containing nicotine in any form among youth, including in e-cigarettes, is unsafe.'
- On 3 April 2017, the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) issued an updated statement on e-cigarettes, to assist Australian consumers and policymakers in understanding the current evidence about the safety and efficacy of e-cigarettes. The NHMRC's statement concluded that action should be taken by health authorities and policy makers to minimise harm to users and bystanders, and to protect vulnerable groups such as young people, until evidence of safety, quality and efficacy of e-cigarettes can be produced. The NHMRC's statement also notes that:
    - While e-cigarettes may expose users to fewer toxic chemicals than conventional tobacco cigarettes, the extent to which this reduces harm to the user has not been determined;
    - E-cigarettes may expose users to chemicals and toxins at levels that have the potential to cause adverse health effects. There is growing evidence to suggest that the long-term inhalation of flavourings used in most e-liquids is likely to pose a risk to health;
    - There is currently insufficient evidence to conclude whether e-cigarettes can assist smokers to quit;
    - There is some evidence to suggest that e-cigarette use in non-smokers is associated with future uptake of tobacco cigarette smoking; and
    - There are concerns that the potential benefits of e-cigarettes in reducing harm to smokers may be outweighed by the risks that they may undermine tobacco control efforts.

Principles that Underpin the Current Policy and Regulatory Approach

1. Evidence-based.

- The current evidence base supports maintaining and, where appropriate, strengthening the current controls that apply to the marketing and use of e-cigarettes in Australia.
- Decisions should take into account the conclusions reached by credible health and scientific agencies in relation to the interpretation and advice about that evidence, including for example the WHO, the NHMRC and the US Surgeon General.[2]
- A notable example is the Therapeutic Goods Administration's (TGA's) scheduling legislation and underlying decision making processes which are informed by relevant evidence and provide a robust mechanism to balance potential risks and benefits of substances such as nicotine for use in e-cigarettes.
- The TGA's consideration and final decision on an application to allow nicotine for use in e-cigarettes to be commercially sold in Australia during 2016 and early 2017, provides a valuable analysis to guide action (Scheduling delegate's final decisions, March 2017).
- Health claims for e-cigarettes, such as that they are effective smoking cessation aids or safe alternatives to conventional tobacco products, should be rejected by health authorities in the absence of robust supporting scientific evidence to substantiate these claims.

2. Relevant to Australia's national circumstances.

- The appropriate policy and regulatory response to e-cigarettes should take into account Australia's national circumstances, including in the context of the existing approaches taken by the Australian and state and territory governments to reduce tobacco smoking prevalence and its associated harms and costs. Australia's favourable progress in tobacco control to date is also an important factor.
- Current and future approaches taken by other countries to e-cigarettes are relevant to the formulation of potential national policy and regulatory responses to these products. At present, there is no international consensus on the most appropriate policy response or regulatory framework for e-cigarettes. Current and planned regulatory approaches vary considerably and across countries, ranging from treatment as tobacco products, poisons, medicines (including medical devices), and consumer products. Additionally, in some countries, the sale of e-cigarettes is prohibited, while in many developing countries, it is likely that minimal or no regulatory controls apply.

3. Precautionary approach.

- This acknowledges the potential risks associated with the marketing and use of e-cigarettes.
- The precautionary approach encourages action to prevent harm when there is scientific uncertainty and until a body of evidence establishes the requirement for alternative regulation. This includes the lack of conclusive evidence around the safety risks posed to users by the unknown inhalation toxicity of nicotine and other chemicals used with e-cigarettes, passive exposure to e-cigarette vapour, risks associated with child poisoning, and issues around quality control and efficacy.
- The precautionary approach also takes into account the broader risks that e-cigarettes may pose to population health, namely their potential to disrupt the decline in tobacco use in Australia.

4. Protecting public health gains.

- While there have been significant gains made in reducing smoking rates and reducing exposure to tobacco smoke and smoking culture in Australia, an increase in e-cigarette marketing and use may undermine tobacco control success by establishing new cohorts with nicotine dependence, renormalising smoking, encouraging dual use of tobacco and e-cigarettes, and discouraging quitting.
- Policy and regulatory decisions on e-cigarettes should aim to minimise the proliferation of e-cigarette marketing and use, particularly among young people while maximising the impact of effective tobacco control measures.
- Policy and regulation for e-cigarettes should aim to protect public health gains in relation to smoking prevalence as well as smoke-free culture, including smoke-free areas and other measures that have contributed to the continued denormalisation of smoking in Australia.

5. Protecting public health policy from all commercial and other vested interests related to e-cigarettes, including interests of the tobacco industry.

- This acknowledges Australia's obligations under Article 5.3 of the WHO FCTC, to which Australia is a party. Under Article 5.3 of the WHO FCTC, parties are obliged to act to protect their public health policies with respect to tobacco control from commercial and other vested interests of the tobacco industry, in accordance with national law.

6. Legal clarity to the public.

- Information from a range of sources highlights that there may be some confusion to users, retailers, employers and the general public about the legality of e-cigarettes and/or nicotine, especially in terms of the regulations that apply to their importation, marketing (including sale) and use.
- It is important that Governments provide clarity to the public about their legal obligations in relation to these products.
- The commercial supply of nicotine for use in e-cigarettes is prohibited under all state and territory poisons legislation.

7. Complementary with jurisdictional regulation and existing health and social policy frameworks.

- National policy and regulation of e-cigarettes and nicotine should aim to complement jurisdictional legislation, to the greatest degree possible.
- It is also important that any action taken at a national or jurisdictional level for e-cigarettes and nicotine supports existing health and social policy frameworks. These include but are not limited to the WHO FCTC (and also including recent decisions of the Conference of the Parties to the WHO FCTC as noted above) the National Drug Strategy 2017-2026, the National Tobacco Strategy 2012-2018 and the Scheduling Policy Framework.

[1] Otherwise known as electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS) or personal vaporisers.

[2] In November 2016, the seventh session of the Conference of the Parties to the WHO Framework Convention on Tobacco Control (WHO FCTC) invited Parties to consider applying regulatory measures to 'prohibit or restrict the manufacture, importation, distribution, presentation, sale and use of ENDS/ENNDS, as appropriate to their national laws and public health objectives'. Further information is available at available at: www.who.int/fctc/cop/cop7/FCTC_COP7_9_EN.pdf?ua=1.

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2.1 Nicotine

Part A - Final decisions on matters referred to an expert advisory committee

Joint Advisory Committee on Chemicals and Medicines Scheduling (ACCS-ACMS #14)

2.1 Nicotine

In this section: Referred scheduling proposal | Scheduling application | Current scheduling status | Relevant scheduling history | Australian regulatory information | International regulations | Substance summary | Pre-meeting public submissions | Summary of Joint ACCS-ACMS advice to the delegate | Delegates' considerations | Delegates' interim decision | Public submissions on the interim decision | Delegates' final decision

Referred scheduling proposal

An applicant has proposed to exempt nicotine from Schedule 7 at concentrations of 3.6 per cent or less of nicotine for self-administration with an electronic nicotine delivery system ('personal vaporiser' or 'electronic cigarette') for the purpose of tobacco harm reduction.

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State/Territory scheduling information

Scheduling application

This was a general application. The applicant's proposed amendments to the Poisons Standard are as follows:

Schedule 7 - Proposed amendment

NICOTINE **except**:

a. when included in Schedule 6;
b. in preparations for human therapeutic use; or
c. in tobacco prepared and packed for smoking; **or**
d. in preparations for use as a substitute for tobacco when packed and labelled:
    i. for use in an electronic nicotine delivery system (ENDS)
    ii. nicotine concentration up to 3.6%
    iii. maximum nicotine per container: 900 mg
    iv. in a child resistant container
    v. labelled with the concentration of nicotine and other ingredients
    vi. labelled with the statement 'Keep out of reach of children'
    vii. labelled with the statement 'Not to be sold to a person under the age of 18 years'.

The applicant's reasons for the request are as follows:

- Harm reduction is a well-documented strategy to reduce the harm of behaviour by substituting it with a less harmful behaviour. Tobacco harm reduction provides an alternative pathway for smokers who are unable or unwilling to quit nicotine. Tobacco harm reduction has huge potential to prevent death and disability from tobacco and reduce health inequalities.
- The scheduling of nicotine was considered by the National Drugs and Poisons committee (NDPSC) in October 2008. The proposed amendment was to exclude nicotine from Schedule 7 'in electronic cigarettes prepared

Schedule 7 in electronic cigarettes prepared and packed as an alternative to traditional smoking'. The committee agreed that the current scheduling remained appropriate and that the Schedule 7 parent entry for nicotine should remain unchanged (NDPSC Oct 2008).

- The applicant asserts since that earlier consideration there has been considerable development in the public health understanding, smoker adoption and regulation of these products globally. This application will update the committee on these developments, with the conclusion that the scheduling of nicotine in Australia for non-therapeutic purposes should be amended.

Current scheduling status

Nicotine is currently listed in the Poisons Standard in Schedules 7, 6 and 4, Appendix F (Part 3), and Appendix J (Part 2) as follows:

Schedule 7

NICOTINE **except**:

a. when included in Schedule 6;
b. in preparations for human therapeutic use; or
c. in tobacco prepared and packed for smoking.

Schedule 6

NICOTINE in preparations containing 3 per cent or less of nicotine when labelled and packed for the treatment of animals.

Schedule 4

NICOTINE in preparations for human therapeutic use **except** for use as an aid in withdrawal from tobacco smoking in preparations for oromucosal or transdermal use.

Appendix F, Part 3 – NICOTINE **except** when in tobacco

Safety directions: 1 (Avoid contact with eyes), 4 (Avoid contact with skin).

Appendix J, Part 2 - NICOTINE

Condition: 1 (Not to be available **except** to authorised or licensed persons).

Relevant scheduling history

In June 1991, the Drugs and Poisons Schedule Standing committee (DPSSC) amended the Schedule 4 entry for nicotine to include all preparations (except Schedule 3 chewing tablets) which could be used as an aid in smoking cessation, containing between 2 and 4 mg of nicotine or roll-on devices with 0.65 per cent or less of nicotine e.g. transdermal patches.

In August 1993, the National Drugs and Poisons Schedule committee (NDPSC) rejected a proposal to have 2 mg sublingual tablets rescheduled from Schedule 3 to Schedule 2 and 4 mg sublingual tablets rescheduled from Schedule 4 to Schedule 3.

In November 1993, the NDPSC agreed that Schedule 4 remained appropriate for patch formulations. Subsequently, in November 1997, transdermal patches were included in Schedule 3.

In February 1997, the NDPSC rescheduled nicotine 2 mg chewable tablets to Schedule 2. However, committee decided that the higher dosage (4 mg) should only be rescheduled to Schedule 3 to facilitate the counselling of heavy smokers by a pharmacist.

In August 1998, the NDPSC agreed to the inclusion of nicotine gum and transdermal patches in Appendix H.

In November 1998, the NDPSC considered down-scheduling nicotine for inhalation, when packed in cartridges for use as an aid in withdrawal from tobacco smoking, from Schedule 4 to Schedule 3 and decided that Schedule 3 was appropriate. The NDPSC noted that this form of oral inhalation was similar in many respects to the chewing gum, being absorbed mainly in the mouth and throat. The data provided indicated that nicotine plasma levels obtained via the inhaler were similar to those obtained with the 2 mg chewing gum.

In February 1999, the NDPSC amended this Schedule 3 nicotine entry to 'Nicotine as an aid in withdrawal from tobacco smoking in preparations for inhalation or sublingual use'. In August 2001, the NDPSC agreed that nicotine lozenges would have a comparable safety profile to that of sublingual tablets, and so it was appropriate to also include lozenges in Schedule 3. Subsequently, lozenge-preparations were down scheduled to Schedule 2 in June 2003. In February 2002, nicotine inhalers were rescheduled from Schedule 3 to Schedule 2.

In February 2010, the NDPSC considered an application to broaden the exemptions for specified NRT buccal dosage formats i.e. chewing gum and lozenges, to buccal preparations in general. The NDPSC decided to only down-schedule oromucosal sprays and did not support an exemption for oromucosal preparations in general, noting that this could potentially include preparations such as mouthwashes. The NDPSC was of the opinion that there was insufficient data for such a broad exemption.

In June 2010, the NDPSC considered a post-meeting submission regarding the February 2010 decision to exempt nicotine preparations for oral mucosal spray use from scheduling. The committee confirmed the February 2010 resolution (2010/58-20) to amend the scheduling of nicotine to exempt oromucosal spray use as an aid in withdrawal from tobacco smoking. The committee agreed that this decision should be referred to a delegate under the new scheduling arrangements commencing 1 July 2010 for consideration of inclusion into the first instrument under these new arrangements with an implementation date of 1 September 2010.

In June 2011, the ACMS considered a proposal to amend the Schedule 4 entry to exempt from scheduling when used for human therapeutic use as an aid in withdrawal from tobacco smoking: (i) nicotine oromucosal film; and (ii) nicotine inhalation cartridges for oromucosal use. These proposed exemptions were similar to the exemptions for nicotine in chewing gums, lozenges, and preparations for sublingual, transdermal or oromucosal spray use when used as an aid in withdrawal from tobacco smoking.

ACMS advised that the Schedule 4 exemption for nicotine in preparations for human therapeutic use be extended to include all oromucosal use and include a definition for *oromucosal* in the Poisons Standard Part 1, Interpretation. The committee advised and the delegate agreed with the deletion of the Schedule 2 nicotine entry (i.e. all nicotine inhalation cartridge preparations for oromucosal use as aids in withdrawal from tobacco smoking would become exempt with any other inhalation preparations for human therapeutic use being captured by Schedule 4). Further, the delegate extended the scheduling exemption for nicotine in preparations for human therapeutic use to include all oromucosal use (to harmonise with the New Zealand scheduling of nicotine for human therapeutic use). The decisions were implemented on 1 January 2012.

Australian regulatory information

Electronic Nicotine Delivery Systems (ENDS) are also known as e-cigarettes, personal vaporisers and vape pens. Nicotine for human consumption is listed in Schedule 4 in the Poisons Standard, except when used as an aid in the withdrawal from tobacco smoking in preparations intended for oromucosal or transdermal use (e.g. nicotine patches, gum or mouth sprays). Nicotine is in Schedule 7, except in preparations for human therapeutic use or in tobacco prepared and packed for smoking. There are no restrictions on importation, but individuals may commit an offence under state and territory laws when they take possession of, use or import nicotine.

In the states and territories, it is an offence to manufacture, sell or supply nicotine as Schedule 7 poison without a licence or specific authorisation. This means e-cigarettes containing nicotine cannot be sold in any Australian state or territory. Nicotine can be imported by an

sold in any Australian state or territory. Nicotine can be imported by an individual for use as an unapproved therapeutic good (e.g. a smoking cessation aid), but the importer must hold a prescription from an Australian registered medical practitioner and only import not more than 3 months' supply at any one time. The total quantity imported in a 12-month period cannot exceed 15 months' supply of the product at the maximum dose recommended by the manufacturer. The purchase and possession of nicotine by individuals are not regulated by Commonwealth legislation, except for importation as allowed under Commonwealth law.

Non-nicotine e-cigarettes are currently not regulated as a therapeutic good under the Commonwealth *Therapeutic Goods Act*. To date, none have been approved by the TGA for registration as a medical device (AFP Vol. 44, June 2016).

In April 2015, the Commonwealth Department of Health engaged the University of Sydney (in partnership with the Cancer Council New South Wales) to explore options to minimise the risks associated with the marketing and use of ENDS in Australia. The project was initiated under the auspices of the Intergovernmental committee on Drugs (IGCD) which reports to the Australian Health Ministers Advisory Council Mental Health, Drug and Alcohol Principal committee. The IGCD nominated that the Department of Health act as the lead agency to oversee the project.

The outcomes of the project are to inform policy options for ENDS (with or without nicotine) that may be considered separately or in coordination by the Commonwealth, state and territory governments. The project is due to report in mid-2016. The Tobacco Control Policy Section has indicated that the report is imminent. However, the broader dissemination of the report will be a matter for the IGCD. At this time it is unknown when the IGCD will be meeting to discuss this report.

International regulations

UK: The 2016 UK guidance policy on regulation of e-cigarettes is available through the following link https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products.

NZ: In August 2016, the NZ Ministry of Health released a consultation document, considering policy options for the regulation of electronic cigarettes and agreeing in principle to allowing the sale of nicotine e-cigarettes as a consumer product. This consultation is attached and is in TRIM at R16/613417.

USA: The USA National Institute on Drug Abuse includes information on e-cigarettes at https://www.drugabuse.gov/publications/drugfacts/electronic-cigarettes-e-cigarettes.

Information on the US FDA ruling on e-cigarettes is available at

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm4
and US FDA labelling information on vaporisers, e-cigarettes and ENDS is at
http://www.fda.gov/tobaccoproducts/labeling/productsingredientscomp

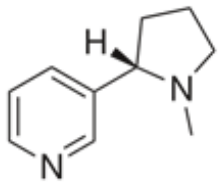
Substance summary

Nicotine is a liquid alkaloid obtained from the dried leaves of the tobacco plant, *Nicotiana tabacum* and related species (Solanaceae). Tobacco leaves contain 0.5 to 8% of nicotine combined as malate or citrate. Nicotine is a colourless or brownish, volatile, hygroscopic, viscous liquid. Soluble in water and; miscible with dehydrated alcohol.

Table 2.1: Chemical information

Large table warning

- This table is large, and may need to be scrolled sideways to view all its content.
- You can also open this table in a new window.

Property	Nicotine
CAS No.	54-11-5
Chemical name	3-[(2*S*)-1-Methylpyrrolidin-2-yl]pyridine; (−)-1-Methyl-2-(3-pyridyl)pyrrolidine; (S)-3-(1-Methyl-2-pyrrolidinyl)pyridine
Chemical structure	
Molecular formula	$C_{10}H_{14}N_2$
Molecular weight	162.2 g/mol

When smoked, nicotine is distilled from burning tobacco and carried on tar droplets (particulate matter), which are inhaled. Nicotine has a plasma half-life of approximately 2 hours. It is metabolised in the liver primarily by the CYP2A6 enzyme into cotinine which is excreted by the kidneys. Nicotine used in nicotine solutions for e-cigarettes is extracted from tobacco leaves.

The toxicity of other ingredients inhaled in solutions used in e-cigarettes

The toxicity of other ingredients inhaled in solutions used in e-cigarettes was not addressed in this application. The Applicant states that other chemicals in e-cigarette vapour include volatile organic compounds, carbonyls, aldehydes, tobacco-specific nitrosamines (TSNAs) and metal particles.

Pre-meeting public submissions

Of the 71 public submissions received, 54 supported and 17 opposed the proposal.

The 54 submissions in support of the proposal were from consumers (35), business owners or manufactures (6), peak bodies (2), advocacy groups (3), medical professionals (7) and a consultant (1).

The main points supporting the proposal were as follows:

- Personal accounts of quitting tobacco or reduced nicotine intake with positive health benefits using e-liquids containing nicotine when other nicotine therapies were unsuccessful or experienced side effects.
- International evidence that e-cigarettes reduce smoking and help smokers quit smoking. Consider that e-cigarettes work because they are pleasurable and address both the nicotine and habit aspect of smoking.
- Consumers can access harm reduction measures. Vaping is less harmful than smoking and is a significant harm reducer for smokers. Nicotine in ENDS may contain small amounts of other chemicals including volatile organic compounds, carbonyls, aldehydes, tobacco-specific nitrosamines (TSNAs) and metal particles. However, research indicates that they are present at much lower levels than in cigarette smoke. Use of ENDS reduces toxin intake.
- Nicotine is already approved in gums, lozenges, patches, inhalers and cigarettes.
- The current laws are confusing and mixed in Australia. Although the use of nicotine in vaping solutions is illegal, it is commonplace. Consumers struggle to understand why nicotine is hard to obtain, given cigarettes are easy to obtain. Suggest decriminalising possession of e-liquid nicotine, making it a consumer product at strength applied for in the application with availability through responsible retailers. By decriminalising, the risk associated with grey and black market unregulated supply chain would be mitigated.
- Consumers are concerned about importing products from overseas, the uncertainty of these products, the restrictions and breaking laws if vaping and potentially driving vaping consumers back to smoking as it is easier to go to the nearest store and obtain cigarettes.

- Consumers including minors can currently obtain e-liquid containing nicotine online from overseas, without responsible retailing to sell the products to adult consumers. Those without internet access and those uncomfortable with buying online are excluded from a harm reduction strategy which has been very successful for many people. As "disadvantaged groups in the population are more likely to take up and continue smoking" (Trends in the prevalence of smoking by socio-economic status), the very people who could be most helped by having low-strength nicotine available are those least likely to be able to access it.
- Suggestions were provided that these should have correct labelling displaying relevant consumer information and warnings relating to use e.g. unsuitability for pregnant and breast feeding women.
- The UK Royal College of Physicians report Nicotine Without Smoke: Tobacco Harm Reduction states 'A risk-averse, precautionary approach to e-cigarette regulation can be proposed as a means of minimizing the risk of avoidable harm, e.g. exposure to toxins in e-cigarette vapour, renormalisation, gateway progression to smoking, or other real or potential risks. However, if this approach also makes e-cigarettes less easily accessible, less palatable or acceptable, more expensive, less consumer friendly or pharmacologically less effective, or inhibits innovation and development of new and improved products, then it causes harm by perpetuating smoking.' The UK Royal College of Physicians have stated that vaping is *at least* 95% safer than smoking and recommend doctors advising patients to switch to vaping.
- The Framework Convention on Tobacco Control Article 1(d) states "tobacco control" means a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke; it seems that Australia is not fulfilling its FCTC obligations in providing access to the harm reduction strategies outlined in article 1(d).
- ENDS are available in New Zealand. Expected changes in New Zealand which would legalise availability of nicotine-containing e-liquids would likely create a problem with illicit product importation if Australia's regulations do not change. Consideration should be given to the emerging regulatory framework for e-cigarettes in New Zealand.
- Overseas these products are sold OTC - overseas research (UK) indicates that the majority of vapers are in ex-smokers and only 0.3% of never smokers used e-cigarettes in 2015 (similar to nicotine replacement therapy 0.1%). Public Health England has endorsed vaping as safer than smoking. Australia should harmonise with the UK, USA and NZ.
- In France, the High Council on Public Health has endorsed

- In France, the High Council on Public Health has endorsed electronic cigarettes as a cessation tool.
- In Belgium the Superior Health Council has stated that electronic cigarettes are a less harmful alternative to tobacco (a position subsequently endorsed by the Health Ministry).
- In normal conditions of use, toxin levels in inhaled ENDS aerosol are below prescribed limit values for occupational exposure, in which case significant long-term harm is unlikely.
- Lethal overdose of nicotine is rare as nicotine is an emetic and any ingestion of liquid nicotine diluent, such as that used for ENDS would result in vomiting.
- Nicotine is the main psychoactive agent in tobacco, it has relatively minor health effects. It is not a carcinogen, does not cause respiratory disease and has only minor cardiovascular effects.
- Regarding the uptake of "vaping" in previously non-smoking youth, the available evidence does not support the "gateway hypothesis" that ENDS encourages nicotine addiction or uptake by youth. In the UK, daily ENDS use in youth is almost exclusively confined to those who already use combustible tobacco daily and regularly. Less than 0.2% of youth who have never smoked combustible tobacco have taken up vaping and there is no evidence of progression to smoking in this cohort.
- Abuse in children: as almost all minors who have used an e-cigarette with nicotinated e-liquid had also tried at least one cigarette. States that the majority of US youth who use vaporisers and e-cigarettes do not vape nicotine.
- Nicotine dependence in youth develops rapidly and over 50% of those youth who smoke daily are already nicotine dependent. Young people who are already smoking can reduce their harm by switching to ENDS by 95%, as was shown in the Public Health UK Report.
- Low concentration nicotine has a proven safety record and is currently widely available as Nicotine Replacement Therapy. The proposed low concentrations present no significant risks. Low risks can be mitigated by packaging and labelling requirements.
- Anti-tobacco restrictions should not be extrapolated to low concentration nicotine use.
- Many health professionals believe that the health risk of consuming nicotine in low dosages (as per electronic cigarettes) is about as harmful to your health as drinking a cup of coffee.
- One user has found the sweet flavours satisfy urges to eat sugary foods.
- No quantifiable harm for those in the vicinity of those vaping. Regarding second hand exposure concerns, at the Public Health UK report included that passive exposure to vapour have generally

concluded that the risk to bystanders is very small and that Public Health England found that "ENDS release negligible levels of nicotine into ambient air with no health risks to bystanders".

- Australia's smoking rates amongst socially disadvantaged groups, particularly people with mental illness have remained unacceptably high. In the US, over 40% of tobacco sales are to people with a mental illness and this figure has been estimated to be even higher in Australia. Most of the 25-year mortality gap between people with schizophrenia and the general population is directly attributable to smoking. People with mental illness smoke in much higher rates than the general population, and the poor health outcomes reported in research are typically associated with smoking related harms. People with mental illness should be offered the opportunity to reduce or quit smoking using e-cigarettes. Existing nicotine replacement therapies have very poor efficacy and they are often costly, not at all affordable for people on a disability pension. E-cigarettes by comparison are very low cost, which increases the likelihood of their uptake by this population.
- Liquid nicotine should be supplied to agreed specifications in Australia by an accredited manufacturer and dispensed by an accredited Australian pharmacist. This would ensure a range of safeguards in regard to the supply and quality of nicotine in Australia
- In regard to the Personal Importation Scheme, the TGA website states "such therapeutic goods may not be approved for supply in Australia, and this means there are no guarantees about their safety or quality." Considers that this is an untenable situation in regard to a substance like liquid nicotine given emerging trends in e-cigarette use, vaping and smoking cessation considerations in Australia.
- There is a strong public health, ethical and pragmatic case to amend the schedule and to allow Australians access to much less risky ways to consume nicotine than smoking.
- Scientific evidence suggests negative effects of use in the long term are unlikely - significant drops (similar to cold turkey quitters) in biomarkers of smokers who switched to vaping. Stable, long term improvements in asthma symptoms have been found in smokers who switch to electronic cigarettes which demonstrate a significant level of harm reversal.
- The 3.6% is on the conservative side, some experts recommend stronger doses when attempting to quit nicotine altogether.
- Nicotine Quickmist® can be purchased at supermarkets and deliver 1 mg of nicotine per spray and each can has 150 sprays. These can be bought easily by anyone (even young adults).
- Nicotine toxicity has been misconceived in both popular press and

Nicotine toxicity has been misconceived in both popular press and general community perception, and even in some scientific sectors, with a lethal dose often quoted to be as little as 60 mg. Bernd Mayer[17] provides an historical perspective of this misconception, and provides a summary of research including clinical trials on animals, as well as investigations into inadvertent and intentional overdoses, and concludes that a careful estimate of the LD50 for nicotine is 0.5 g, or 6.5 mg/kg, which for the 36 mg/mL concentration proposed for approval, is theoretically approximately 15mL. But this would be almost impossible to reach the bloodstream in its entirety, due to the severe vomiting and diarrhoea such a dose would immediately arouse. Most recorded suicide attempts using nicotine have failed for this reason, with little or no long term effects.

- Vapers self-regulate nicotine dosage like smokers using tobacco products by reducing or stopping puffs taken on the basis of early symptoms of overdose such as headache, dizziness and nausea.
- Legalising nicotine-containing electronic cigarettes will make their manufacture, presentation and sale safer for consumers by:
    - reducing consumers' dependence on the unlawful or black market products proliferating in Australia
    - shaping a regulatory regime ensuring that all products on the market comply with appropriate standards of quality and safety
- The costs associated with listing nicotine vaping products on the ARTG is a disincentive to manufacturers to pursue with option of nicotine delivery.
- While the possession of nicotine solution remains illegal, there is no consumer regulation of these products - products are mislabelled to reduce detection. Current policy drives low-dose nicotine users underground, to obtain supplies from overseas or from merchants who do not label the nicotine content of the vaping fluid.
- Tax on e-cigarettes overseas is low compared to traditional cigarettes, this is incentive to switch
- ENDS has a 50-70% success rate of quitting tobacco smoking while having positive health effects on the body.
- Nicotine solution of 3.6% or less is also not enough product to cause a deadly result from ingestion as it takes 500-1000mg of pure Nicotine for death and the concentration level is too low.
- We should be making it easier, not harder, for people to access products that might help them quit, and provide more options.
- Potential for harm outweighs the potential for abuse
- One supporting submission also proposed a 3% allowance for animal use, moving it from Schedule 6 (Poison) to Schedule 5

(Caution) together with a Schedule 5 entry for nicotine in preparations containing 3.6% or less of nicotine when labelled and packed for use in e-cigarettes (electronic nicotine delivery systems or ENDS) on the basis that at the 3.6% level of dilution it should be used with caution, but it was not considered a dangerous poison.

The 17 submissions that do not support the proposal were from academia (1), Government Health Departments (7), non-government organisations (4) and peak bodies (5).

The main points opposing the proposal were as follows:

- The risks and benefits of the use of a substance
    - Given that nicotine is readily absorbed through the skin, nicotine available in liquid form for use in e-cigarettes poses a significant risk of acute nicotine poisoning. Furthermore, there is serious risk of acute nicotine poisoning for children which can occur through ingestion of products containing nicotine. There has been evidence of this internationally in the USA and UK.
    - The safety and long term health effects of these products are unknown, and any potential benefits are still to be determined and may be outweighed by the risks posed by their widespread use in the community.
    - The limited evidence to indicate that electronic cigarettes are effective nicotine cessation aids does not justify the risks posed by these products.
    - Research has shown that most people who use electronic cigarettes do not quit smoking conventional tobacco products, resulting in dual-use. Dual use results in a much smaller benefit on overall survival compared to quitting smoking entirely.
    - The chemical combinations used in electronic cigarettes have adverse impacts on pulmonary function and the cardiovascular system.
    - Second-hand e-cigarette vapour contains pollutants at levels above background levels and therefore is associated with negative health effects.
    - Nicotine is highly addictive. Permitting nicotine as an ingredient in e-cigarettes increases the risk of individuals, who would have otherwise been unlikely to become tobacco smokers, developing nicotine addiction.
    - The inherent risk of promoting ENDS as an option for smoking harm reduction follows the massive failures of past harm reduction interventions such as cigarette filters and 'light' and 'mild' product descriptors.
    - Through heavy marketing and advertising strategies, there is

    - Through heavy marketing and advertising strategies, there is a possibility that smoking may once again become socially acceptable.

- The purposes for which a substance is to be used and the extent of use of a substance
    - There is limited and highly conflicting evidence internationally regarding the effectiveness of using e-cigarettes as a smoking cessation aid (with or without nicotine). This research is in its infancy with some research groups stating that smokers who used e-cigs were less likely to quit smoking tobacco than those who did not 18, while others state that e-cigarettes helped smokers to stop smoking tobacco long term and reduce the amount smoked by half19.
    - Australia's National Health and Medical Research Council and the World Health Organization (WHO) does not currently consider e-cigarettes to be a legitimate tobacco cessation therapy as 'no rigorous peer-reviewed studies have been conducted to show that e-cigarettes are a safe, effective, Nicotine Replacement Therapy.
    - Availability of alternative smoking cessation aids, such as nicotine replacement therapies (e.g. gum and patches), have been rigorously assessed for efficacy and safety and have been approved by the TGA. However, e-cigarettes may be more attractive to smokers than existing nicotine replacement products, due to their lower cost, mimicry of the smoking action and potential better nicotine delivery system. These factors may discourage smokers from quitting.
    - E-cigarettes containing nicotine may be marketed as a way to improve social status rather than for smoking cessation, which may increase the appeal of the product to non-tobacco-smoking youth.
    - The extent of use of e-cigarettes containing nicotine is at the discretion of the user, which may increase the incidence of nicotine addiction and nicotine poisoning.
    - Once a thorough assessment has been completed into the safety and efficacy of nicotine-containing e-cigarettes as a smoking cessation aid, these products should be restricted to prescription only.
    - Evidence suggests that e-cigarettes undermine the intent of smoke-free laws, as many smokers use non-nicotine e-cigarettes in legislated smoke-free areas to maintain their smoking behaviour.

- The toxicity of a substance
    - Nicotine is highly toxic and poses a number of health hazards including adverse cardiovascular, respiratory, renal and reproductive effects. Despite the lower dose proposed, effects

reproductive effects. Despite the lower dose proposed, effects on cardiovascular system and the risk of developing cardiovascular and respiratory diseases are nearly as large as smoking traditional tobacco products.

    - Nicotine can be absorbed through the skin and poisoning may result in symptoms such as nausea, vomiting, seizures, abdominal pain, fluid build-up in the airways (bronchorrhea), high blood pressure, ataxia, rapid heart rate, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death (with large doses - medium lethal dose 6.5-13 mg/kg).
    - Evidence from the International Agency for Research on Cancer (the WHO's source for information about cancer) suggests that nicotine is associated with DNA damage and other pathways of carcinogenesis.
    - Human and animal data suggest that nicotine exposure during periods of developmental vulnerability (foetal through adolescent stages) has multiple adverse health consequences, including impaired foetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents, which may result have future mental health implications for the exposed child.
    - The claim that 'ENDS are 95% less harmful than smoking' was derived from the guesses of a consensus group (whose provenance has been heavily questioned), rather than from an appropriately conducted and peer-reviewed, scientific research study.

- The dosage, formulation, labelling, packaging and presentation of a substance
    - The wide variation in available devices and cartridge fluids make it difficult to quantify the safety of all e-cigarettes.
    - Exemption from scheduling may mean there will be less control over standards and quality control of preparations, labelling and packaging considerations and the application of warning statements.
    - There is a lack of evidence to support a safe dose. Some submitters suggest that the proposed 3.6% is too high. This concentration equates to approximately 36 mg of nicotine per ml of liquid, in comparison to the 13-30 mg of nicotine in a single cigarette. Furthermore, the dosage of nicotine administered through an e-cigarette, and frequency of use, is largely at the discretion of the user. These factors may lead to an increased incidence of addiction and poisoning, especially in children.
    - Labelling
        - It is important that health risks of nicotine be clearly

labelled and that the packaging be childproof and not be designed to appeal to young people.

        - Some e-liquids that do not list nicotine on the label have been found, upon scientific testing by State and Territory health authorities, to contain nicotine. The Australian Competition and Consumer Commission has recently commenced proceedings in the Federal Court against two a-cigarette retailers alleging false or misleading representations and misleading conduct by making statements on their websites that their ENDS products did not contain toxic chemicals

    - Formulation
        - Allowing open access to ENDS nicotine supplies will result in large-scale respiratory exposure to thousands of e-cigarette additives (such as propylene glycol, glycerol, ethylene glycol and flavourings) which have never been assessed for safety via inhalation in aerosol form (whether directly of via second-hand vapour).
        - When heated, one of the common e-cigarette additives, propylene glycol, can form the carcinogenic derivative propylene oxide.
        - Flavoured e-cigarettes (e.g. bubble gum, fruit and confectionary flavours), with or without nicotine content, could appeal to adolescents (leading to rapid uptake of tobacco smoking) and to children (leading to toxicity).

    - Device safety
        - There are concerns regarding device safety and a growing amount of global evidence to suggest that ENDs devices carry a risk of battery failure, low-quality materials, manufacturing flaws and malfunction, leading in some cases to explosions, fire and injury.

- The potential for abuse of a substance
    - The practice of 'vaping' a high volume of liquid in order to produce the biggest or most intricate cloud of vapour also creates a risk of inadvertent nicotine poisoning if the e-cigarette used contains nicotine.

- Any other matters that the Secretary considers necessary to protect public health
    - Personal Importation Scheme: A process already exists for individuals to import personal vaporisers and/or liquid nicotine for personal therapeutic use via the TGA's Personal Importation Scheme[20].
    - Gateway to relapse: Risk of gateway to relapse. There is a risk that former tobacco smokers and nicotine addicts may

relapse through the use of e-cigarettes containing nicotine.

- Gateway to tobacco use (in adults and adolescents):
  - International evidence from the USA and UK, indicate that e-cigarettes (regardless of nicotine content) are being used by individuals as a gateway to tobacco use, triggering a new generation of smokers. There is a concern that advertising e-cigarettes will serve to reverse much of the progress that has been made to de-normalise, de-glamorise and reduce tobacco smoking in Australia.
  - There has been a rapid increase in the number of adolescents using e-cigarettes in the USA and UK. In the UK, 20% of British youths (aged 11-15) have used e-cigarettes, 73% of whom are non-smokers. This has been associated with higher incidences of users transitioning onto traditional cigarettes. The US stats indicate that e-cigarette use has increased four-fold in middle and high schoolers from 2011-2012 and that the continual fall in cigarette smoking that has been occurring since at least 1998, stopped in 2014 and 2015.
- Industry bias:
  - The argument that nicotine is all but benign is often advanced by those highly conflicted by commercial interests involved in selling ENDS. Such arguments seldom note the findings of a large body of research into possible adverse effects arising from consumption of nicotine.
  - The long term business model for the ENDS industry must involve seeing cohorts of young people take up vaping, regardless of protests from that industry to the contrary. In the UK where it is illegal to sell ENDS supplies to children, a recent report21 found that 40% of ENDS retailers did so.

Summary of Joint ACCS-ACMS advice to the delegate

The committee advised that the current scheduling of nicotine remains appropriate.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health

The reasons for the advice comprised the following:

- There is a risk of nicotine dependence associated with use of Electronic Nicotine Delivery System (ENDS). The potential for nicotine dependence is much higher with third generation ENDS and is greater than with the nicotine replacement therapy products marketed in Australia. In countries such as the USA where there has been more ready access to ENDS there is some evidence that ENDS use in never-smoking youth may increase the risk of subsequent initiation of cigarettes and other combustible products during the transition to adulthood when the purchase of tobacco products becomes legal. There is some dual use of conventional cigarettes and ENDS in smokers. There is a risk that ENDS will have a negative impact on tobacco control and may re-normalise smoking. If exempt from Schedule 7, availability of ENDS in children may cause an increase in smoking as they transition to adulthood, which raises public health concerns.
- There is little evidence regarding the safety of long term nicotine exposure via ENDS. Exposure to nicotine in adolescents may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The toxicity of long term exposure to nicotine delivered by ENDS is unknown. Long-term exposure to excipients via the ENDS route of exposure is uncertain.
- Nicotine can cause nausea, vomiting, convulsions, bronchorrhoea, high blood pressure, ataxia, tachycardia, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death in overdose.
- The proposed maximum amount of 900 mg of nicotine per pack is within the estimated lower limit causing fatal outcome (500 mg to 1g). There have been reports of unintentional ingestion of ENDS liquid by children with severe outcomes in some cases. The proposed maximum concentration of 36 mg of nicotine per mL is high (the EU Tobacco Product Directive specifies a maximum concentration of 20 mg/mL). The amount of nicotine in 5 mL of a 3.6% solution in ENDS is 180 mg, which would likely cause significant toxicity in a young child (5 mL would be one swallow for a toddler). Child-resistant packaging would reduce the risk of unintentional exposure to the solution in children.
- ENDS is used for Tobacco Harm Reduction, assistance with cessation of smoking and for recreational use. Public health authorities have varying views about the benefits of ENDS to tobacco harm reduction and as an aid in smoking cessation. Currently about 9% of current smokers and recent quitters in Australia use ENDS. Excepting nicotine from Schedule 7 would likely result in increased nicotine exposure via ENDS (based on countries such as the UK and USA where these products are more

widely available, and the increase in Australia in recent years). In the UK 19% of smokers and 8% of ex-smokers currently use ENDS.

- The use of a label warning statement 'not to be sold to a person under the age of 18 years' is not likely to be effective unless there is enforcement of this requirement. There is a risk there will be inappropriate marketing and advertising of nicotine for use with ENDS if nicotine for use with ENDS is exempted from Schedule 7.

Delegates' considerations

The delegates considered the following in regards to this application:

- Scheduling proposal
- Public submissions received
- ACCS-ACMS advice
- Section 52E of the *Therapeutic Goods Act 1989*
- Scheduling Policy Framework (SPF 2015)
- Other relevant information.

Delegates' interim decision

The delegates' interim decision is that the current scheduling of nicotine remains appropriate.

The delegates considered the relevant matters under section 52E (1) of the *Therapeutic Goods Act 1989*: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; (f) any other matters that the Secretary considers necessary to protect the public health.

The reasons for the interim decision are the following:

- The delegates acknowledge and agree with the ACCS-ACMS advice.
- There is a risk of nicotine dependence associated with use of Electronic Nicotine Delivery System (ENDS). The potential for nicotine dependence is much higher with third generation ENDS and is greater than with the nicotine replacement therapy products marketed in Australia. In countries such as the USA where there has been more ready access to ENDS there is some evidence that ENDS use in never-smoking youth may increase the risk of subsequent initiation of cigarettes and other combustible products during the transition to adulthood when the purchase of tobacco products becomes legal. There is some dual use of conventional cigarettes and ENDS in smokers. There are several

published studies showing that youth who initiate smoking with e-cigarettes are about three times more likely to be smoking conventional cigarettes a year later. There is a risk that ENDS will have a negative impact on tobacco control and may re-normalise smoking. If exempt from Schedule 7, availability of ENDS in children may cause an increase in smoking as they transition to adulthood, which raises public health concerns.

- There is little evidence regarding the safety of long term nicotine exposure via ENDS. Exposure to nicotine in adolescents may have long-term consequences for brain development, potentially leading to learning and anxiety disorders. The toxicity of long term exposure to nicotine delivered by ENDS is unknown. Long-term exposure to excipients via the ENDS route of exposure is uncertain.
- Nicotine can cause nausea, vomiting, convulsions, bronchorrhoea, high blood pressure, ataxia, tachycardia, headache, dizziness, confusion, agitation, restlessness, neuromuscular blockade, respiratory failure and death in overdose.
- The dosage, formulation, labelling, packaging and presentation of the nicotine as would occur if the scheduling was amended would allow nicotine to be too accessible as a liquid which has higher risks and requires appropriate controls.
- The proposed maximum amount of 900 mg of nicotine per pack is within the estimated lower limit causing fatal outcome (500 mg to 1g). There have been reports of unintentional ingestion of ENDS liquid by children with severe outcomes in some cases. The proposed maximum concentration of 36 mg of nicotine per mL is high (the EU Tobacco Product Directive specifies a maximum concentration of 20 mg/mL). The amount of nicotine in 5 mL of a 3.6% solution in ENDS is 180 mg, which would likely cause significant toxicity in a young child (5 mL would be one swallow for a toddler). Child-resistant packaging would reduce the risk of unintentional exposure to the solution in children.
- In the USA, accidental poisonings associated with e-cigarettes have increased from one per month in 2010 to 215 per month in 2014 including one death.
- ENDS is used for Tobacco Harm Reduction, assistance with cessation of smoking and for recreational use. Public health authorities have varying views about the benefits of ENDS to tobacco harm reduction and as an aid in smoking cessation. Currently about 9% of current smokers and recent quitters in Australia use ENDS. Excepting nicotine from Schedule 7 would likely result in increased nicotine exposure via ENDS (based on countries such as the UK and USA where these products are more widely available, and the increase in Australia in recent years). In the UK 19% of smokers and 8% of ex-smokers currently use ENDS.

- The use of a label warning statement 'not to be sold to a person under the age of 18 years' is not likely to be effective unless there is enforcement of this requirement. There is a risk there will be inappropriate marketing and advertising of nicotine for use with ENDS if nicotine for use with ENDS is exempted from Schedule 7.

Public submissions on the interim decision

Twenty-one (21) submissions were received. Five supported and 16 opposed the delegate's interim decision.

The main points in support of the proposal were as follows:

- There was support for the decision in light of the *2016 Surgeon General's Report: E-cigarette Use Among Youth and Young Adults*[22]. This report makes several conclusions:
  - E-cigarette use among youth and young adults is a public health concern, being the most popular tobacco product among youth.
  - E-cigarette use strongly associated with tobacco products.
  - Nicotine-containing products, in any form, among youth, are unsafe.
  - E-cigarette aerosol is not harmless and can contain harmful ingredients.
  - Other actions can be taken to reduce tobacco use among youth.
- Reiteration of the points made in pre-meeting consultation included:
  - Allowing open access to ENDS nicotine supplies will result in large-scale respiratory exposure to thousands of e-cigarette additives (such as propylene glycol, glycerol, ethylene glycol and flavourings) which have never been assessed for safety via inhalation in aerosol form (whether directly of via second-hand vapour).
  - When heated, one of the common e-cigarette additives, propylene glycol, can form the carcinogenic derivative propylene oxide.
  - Flavoured e-cigarettes (e.g. bubble gum, fruit and confectionary flavours), with or without nicotine content, could appeal to adolescents (leading to rapid uptake of tobacco smoking) and to children (leading to toxicity).
- The current scheduling remains appropriate and is in line with Australia's obligations under the WHO Framework Convention on Tobacco Control for the prevention and reduction in nicotine addiction.
- The emerging use of 'dripping', particularly in youth in the US, is of

concern due to the user being exposed to higher nicotine levels than those with ENDS use.

- Recent studies since the initiation of public consultation support the interim decision, stating that ENDS use is associated with increased cardiovascular risk, e-liquids may have acute cytotoxic effects on respiratory cells and that ENDS use in youth in the US is on the rise.

The main points in opposition to the proposal were as follows:

- Traditional methods to quit smoking are ineffective. Prescription medicines are not viable due to side effects. Nicotine-containing fluid for e-cigarettes has been successful in quitting; recommends e-cigarettes to other smokers as an effective form of quitting.
- E-cigarettes are cheaper than tobacco.
- E-cigarettes are legal in several jurisdiction in the EU and USA and being considered in others. Australian smokers deserve the same opportunities to reduce their health risks as Europeans or Americans. Consumers demand practical workable regulation of low strength nicotine.
- There is already demand for e-cigarettes in Australia despite the lack of marketing the illegality of nicotine-containing liquid without prescription. Current smokers are obtaining nicotine-containing liquid illegally to combat addiction to tobacco and prohibition is not working. A regulated solution would lessen potential harm of nicotine-containing liquid of e-cigarettes. Concerns regarding nicotine overdosing can be managed through proper regulation.
- The lowest smoking rates in the world are in the countries where e-cigarettes are an alternative nicotine delivery method. Rates of tobacco use will not be able to fall substantially without proper regulation and permission of nicotine in e-cigarettes.
- The benefits of e-cigarettes outweigh the risks. Health risks associated with tobacco come from tar, rather than nicotine. Nicotine in use of ENDS enables a harm-reduction opportunity from smoking-related morbidity and mortality.
- "Dual use" in many cases is a transition stage and not a means to an end.
- Vapers self-regulate and cease when they sense they have had enough nicotine.
- Use of ENDS is supported by Royal College of Physicians and Public Health England. There is a lack of evidence on the safety of long term nicotine exposure via ENDS. Some evidence shows that those who use e-cigarettes over a six month period have fare less toxic and cancer-causing substances than those who use tobacco.
- Rejection of the assertion that use of ENDS leads to tobacco use

among youth, based on several studies from the UK. There is evidence that counters that cited in the interim decision that ENDS use in never-smoking youth increases the risk of tobacco use. If a child who wishes to smoke cannot access an ENDS then they will acquire a tobacco product instead.

- The evidence concerning youth use of e-cigarettes is misrepresented throughout the interim decision. There is no evidence anywhere of harmful gateway effects. Concerns over use of ENDS in youth and over marketing of ENDS can be easily addressed through appropriate restrictions and regulations
- The risks from low-concentrations liquid nicotine in child-proof containers are similar to other potentially poisonous household chemicals.
- Recommendation of child-resistant packaging to reduce potential risks of nicotine-containing e-cigarette liquid.
- The absolute rate of accidental poisonings from liquid nicotine preparations remains low, despite reports they have increased.
- There is enforceable socially-responsible advertising in the UK of ENDS and this should be incorporated into Australian consumer law.
- There is evidence characterising the physics and chemistry of e-cigarette aerosol and cigarette smoke. E-cigarettes create much lower exposures to toxic agents.
- There are no reports of overdoses among regular users. Accidental exposures do happen but they represent a manageable and minor detriment compared to the risks associated with smoking.
- It is unreasonable that one nicotine delivery system is favoured over others, particularly when one permitted system is tobacco. If there is concern, then no bias should be shown for one system over another.

Delegates' final decision

The delegates have confirmed the interim decision and reasons for the decision as no evidence has been received to alter the interim decision. The delegates' final decision is that the scheduling for nicotine remains appropriate.

Reasons for the final decision additional to those provided from the interim decision include:

- The delegates noted the submissions which included some new evidence in support of, and opposing the interim decision. The reasons for the final decision include those reasons for the interim decision and the below reasons as well.
- It is in line with the 2016 United States Surgeon General's Report: E-cigarette Use Among Youth and Young Adults released in

E-cigarette Use Among Youth and Young Adults released in December 2016 which makes several conclusions:
    - E-cigarette use among youth and young adults is a public health concern, being the most popular tobacco product among youth.
    - E-cigarette use strongly associated with tobacco products.
    - The use of Nicotine-containing products in any form in youth is unsafe.
    - E-cigarette aerosol is not harmless and can contain harmful ingredients.
    - Other actions can be taken to reduce tobacco use among youth.
- It is in line with Australia's obligations under the WHO Framework Convention on Tobacco Control for the prevention and reduction in nicotine addiction.
- The Public Health Association of Australia in its submission noted that:
    - *there have been further major reports (including from the US Surgeon General) and publications confirming its appropriateness and raising additional concerns about cardiovascular and other harms; impacts on children and young people; potential to trigger relapse among ex-smokers or those attempting to quit; dual use; cessation outcomes; and tobacco industry use of new products for promotional and lobbying purposes.*
- This was also noted by the Australian Council on Smoking and Health in its submission to the interim decision.
- The fact that e-cigarettes with nicotine are legal in some other jurisdictions in the EU and the USA are not reasons to make nicotine for use in e-cigarettes exempt in Australia, especially with the success in decreasing smoking in Australia without them.
- It is acknowledged there are divergent expert views on the availability of nicotine containing e-cigarettes as was well demonstrated in 2014 with the two letters to the then Director General of the WHO, Margaret Chan, which provided opposite views from a broad range of eminent public health specialists and in the submissions in the initial consultation and following the interim decision.
- Current government policy supports the cessation of smoking rather than harm reduction.
- That current smokers are obtaining nicotine-containing liquid illegally to combat addiction to tobacco is in itself not a valid reason to allow it to be accessed legally.
- It is still possible for an electronic nicotine delivery system to be

approved by the TGA and included on the ARTG for use as an aid to cease smoking, hence giving access to those smokers who wish to cease.

17 Bernd Mayer. How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol . 2014; 88(1): 5-7: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3880486/

18 Grana *et al*. 'E-cigarettes: A Scientific review' *Circulation.* 2014, 129(19), 1972-1986 (Attachment G)

19 McRobbie et al. 'Electronic cigarettes for smoking cessation (Review)' *Cochrane Database of Systematic Reviews*, 2016, 9, CD010216 (Attachment G)

20 Personal importation scheme (https://www.tga.gov.au/personal-importation-scheme)

21 http://www.localgov.co.uk/Retailers-flout-laws-on-selling-e-cigarettes-to-children/41409

22 https://www.cdc.gov/tobacco/data_statistics/sgr/e-cigarettes/pdfs/2016_sgr_entire_report_508.pdf

Category: Scheduling
Tags: ACCS, ACMS
URL: https://www.tga.gov.au/node/736223

Australian Government
National Health and Medical Research Council

NHMRC CEO Statement: Electronic Cigarettes (E-Cigarettes)

Summary

Electronic cigarettes (e-cigarettes, also known as electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS)) are often marketed as a method to assist smokers to quit, or as a 'safe alternative' to conventional tobacco cigarettes. However, there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed.

Key messages

- E-cigarettes may expose users to fewer toxic chemicals than conventional tobacco cigarettes; however the extent to which this reduces harm to the user has not been determined.
- E-cigarettes may expose users to chemicals and toxins such as formaldehyde, heavy metals, particulate matter and flavouring chemicals, at levels that have the potential to cause adverse health effects.
- There is currently insufficient evidence to conclude whether e-cigarettes can assist smokers to quit. Smokers wishing to quit should consult the Quitline or their general practitioner.
- There is some evidence from longitudinal studies to suggest that e-cigarette use in non-smokers is associated with future uptake of tobacco cigarette smoking.
- Health authorities and policy-makers should act to minimise harm to users and bystanders, and to protect vulnerable groups such as young people, until evidence of safety, quality and efficacy can be produced.
- NHMRC is currently funding a number of studies into the safety and efficacy of e-cigarettes.
- Consumers should seek further information about e-cigarettes from reliable sources, such as the relevant State or Territory Health Department or quit smoking services.

E-cigarettes are battery operated devices that heat a liquid (called 'e-liquid') to produce a vapour that users inhale. Although the composition of this liquid varies, it typically contains a range of chemicals, including solvents and flavouring agents, and may or may not contain nicotine. E-cigarettes have evolved as a product group since first entering the market, with products now ranging from early 'first generation' devices that resemble cigarettes, to second and third generation devices that enable users to modify characteristics of the device, such as adjusting the voltage.[1]

This wide variation in products, and the ability of users to customise their vaping experience, makes it difficult to assess the safety and efficacy of e-cigarettes as a group, because the results from research involving one particular product may not be applicable to all e-cigarettes or all users. However, by examining the evidence to identify common findings across a range of different products, or results that are replicated in a number of studies, it is possible to gain some insight into the efficacy of e-cigarettes, their potential harms, and areas where further research is required.

NHMRC recognises the need for high-quality research in this area and is currently funding a number of studies investigating the effects of e-cigarettes.

The following information is provided to assist consumers and policy-makers in understanding the current evidence about the safety and efficacy of e-cigarettes. This information is current at the time of writing but is subject to change as more research becomes available.

Health and safety

Potential health risks

It is widely believed that e-cigarettes are likely to be less harmful than tobacco cigarettes, because they expose users to fewer toxic chemicals.[2, 3, 4] However, there is insufficient evidence to quantify the reduction in risk when e-cigarettes are used instead of tobacco cigarettes.[1, 5] Although a 2014 study reported that e-cigarettes are 95% less harmful than tobacco cigarettes,[6] this finding was based on opinion rather than empirical evidence, and concerns have been raised about potential conflicts of interest.[7, 8] The World Health Organisation has stated that "no specific figure about how much 'safer' the use of these products is compared to smoking can be given any scientific credibility at this time."[1]

E-cigarettes are not likely to be risk free, and may expose users to chemicals and toxins at levels that have the potential to cause health effects. These include solvents such as propylene glycol, glycerol or ethylene glycol, which may form toxic or cancer-causing compounds when vaporised.[9, 10, 11, 12, 13, 14, 15, 16, 17] Although these chemicals are typically found in lower concentrations than in tobacco cigarettes,[3, 4, 10, 15] in some studies e-cigarettes and tobacco cigarettes were found to produce similar levels of formaldehyde,[11, 14] which is classified as a cancer-causing agent.[18] E-cigarette liquids or vapour may also contain potentially harmful chemicals which are not present in smoke from tobacco cigarettes.[1, 11, 19]

While some of the chemicals in e-liquid are also used in food production and are generally considered safe when eaten, this does not mean that these chemicals are safe when inhaled as a vapour directly into the lungs. A number of studies have reported harmful effects when certain flavourings that are approved for use in food production, including cherry, cinnamon and popcorn flavours, are inhaled.[20, 21, 22, 23] There is growing evidence to suggest that the long-term inhalation of flavourings used in most e-liquids is likely to pose a risk to health.[1]

Studies also show that e-cigarettes expose both users and bystanders to particulate matter (very small particles)[16, 24, 25, 26, 27] that may worsen existing illnesses or increase the risk of developing diseases such as cardiovascular or respiratory disease.[28] The World Health Organisation has warned that exposure to any level of particulate matter may be harmful and that levels of exposure should be minimised.[29]

E-cigarettes may also expose users to metals such as aluminium, arsenic, chromium, copper, lead, nickel and tin,[3, 15, 30, 31, 32] with these elements having been detected in e-liquid and in the vapour produced during use. In some cases these metals have been detected at levels greater than, or similar to, those found in tobacco cigarettes.[1, 30]

Adverse events

Studies that have tested e-cigarettes for use as a smoking cessation tool found that users of e-cigarettes typically experience a low rate of adverse events in the short term,[33, 34] with mouth and throat irritation the most commonly reported symptoms. However, more serious adverse events have also been reported, with over 200 incidents of e-cigarettes overheating, catching fire or exploding reported to date in the US and UK alone.[35] In some cases, these events have resulted in life-threatening injury, permanent disfigurement or disability, and major property damage.

The rising popularity of e-cigarette use internationally has also corresponded with an increasing number of reported nicotine poisonings due to exposure to or ingestion of e-liquids.[36, 37, 38, 39, 40, 41, 42] The effects of exposure range from relatively mild, including irritation of the eyes and skin, nausea and vomiting,[36, 37, 40] to severe life-threatening illness,[39] and in some cases, death.[36, 38, 42]

Passive exposure

A recent systematic review of 16 studies concluded that e-cigarette vapour has the potential to pose a health risk to bystanders, although the risk is likely to be lower than that posed by conventional cigarette smoke.[43] However, exposure to certain metals such as nickel and silver may be greater for e-cigarettes than tobacco cigarettes.[43] A 2016 study found that the most common symptoms reported by those passively exposed to e-cigarettes included respiratory difficulties, eye irritation, headache, nausea and sore throat or throat irritation.[44]

Smoking cessation

Experts disagree about whether e-cigarettes may help smokers to quit, or whether they will become 'dual users' of both e-cigarettes and tobacco cigarettes. There is currently insufficient evidence to demonstrate that e-cigarettes are effective in assisting people to quit smoking[1] and no brand of e-cigarette has been approved by the Therapeutic Goods Administration (TGA) for this purpose. Although a 2016 systematic review conducted by the Cochrane Collaboration[33] found some evidence that e-cigarettes with nicotine may assist smokers to quit, the review authors had a low level of confidence in this finding, due to the small volume of evidence. The review also reported results from one study comparing e-cigarettes with nicotine replacement therapy, which found that both methods resulted in similar rates of smoking cessation at 6 months follow-up. However, the reviewers noted that more research is required to enable confidence in these estimates and that further research is likely to change the estimate of effect.[33]

Smokers wishing to quit are advised to consult their general practitioner. First-line treatments include a range of TGA-approved nicotine replacement therapies and prescription medications that have been tested for safety and efficacy. Support and information are also available from the Quitline (13 78 48) or via the Quit Now website (www.quitnow.gov.au).

E-cigarettes and tobacco control policies

Concerns have been raised that the potential benefits of e-cigarettes in reducing harm to smokers may be outweighed by the risks that they may undermine tobacco control efforts. This includes the potential for e-cigarettes to provide a gateway to nicotine addiction or tobacco product use, or that they may renormalise smoking. The appeal of flavoured e-cigarettes to children and adolescents is also of concern, with studies reporting rapid uptake of e-cigarettes among adolescents in many countries, where trend data are available.[45, 46, 47, 48, 49] This provides some cause for concern given uncertainties about the long-term safety of e-cigarettes.

There is some evidence that e-cigarettes could act as a gateway into nicotine addiction or tobacco cigarette smoking. A number of longitudinal studies have reported an association between e-cigarette use in non-smokers and the uptake of tobacco cigarette smoking in the future.[50, 51, 52, 53] This association remained even when the studies controlled for other risk factors that might make people more likely to take up smoking. In some studies, the effect of e-cigarettes on future smoking behaviour was greatest among those who were otherwise at low risk of taking up smoking.[51, 54] A number of studies have also reported an association between e-cigarette use in non-users and future use of marijuana[52] or tobacco products such as hookahs, cigars or pipes.[51, 55, 56]

In view of the above concerns, the World Health Organisation has recommended that policy-makers act to prevent the initiation of e-cigarette use by non-smokers and youth, with special attention given to protecting vulnerable groups.[1]

Manufacturing quality

The manufacturing quality of e-cigarettes is highly variable, with a number of issues relating to quality control reported in the literature. Labelling of e-cigarettes and e-liquids has been found to be incomplete or inaccurate.[57, 58] Products have been found to contain chemicals that were not listed on the label,[57, 58, 59] or to state incorrectly that they did not contain potentially toxic chemicals, despite analyses confirming their presence.[60, 61]

There may also be wide variation between the levels of nicotine declared on packaging and the amount contained in e-liquid.[9, 58, 62, 63, 64, 65] One study that compared identical models of e-cigarettes found that nicotine content varied by up to 20% when the products came from different manufacturing batches, with variation of up to 12% reported for products manufactured in the same batch.[66] Furthermore, some products that are labelled as nicotine free have been found to contain nicotine.[11, 15, 57, 59, 62, 65, 67, 68]

Where can I get more information?

When seeking information about e-cigarettes online, it is important to look at websites that provide a reliable source of information, such as government websites or quit smoking services. Information on websites sponsored by retailers or manufacturers may reflect a commercial interest in promoting the sale of certain products.

Similarly, when reading published research on e-cigarettes it is important to consider whether the authors of the research held any conflicts of interest that could potentially bias their findings, or whether the research was funded by an organisation with a financial interest in the outcomes, such as e-cigarette manufacturers.[69]

The following websites may provide further information of use to consumers:

Evidence-based reports

World Health Organisation – *Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)*
http://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf

Information, fact sheets and FAQs from government departments

ACT Health – *Electronic Cigarettes*
http://www.health.act.gov.au/public-information/public-health/tobacco-and-smoke-free/electronic-cigarettes

New South Wales Department of Health – *Electronic Cigarettes*
http://www.health.nsw.gov.au/tobacco/Pages/electronic-cigarettes.aspx

Product Safety Australia – *Electronic Cigarette Safety*
http://www.productsafety.gov.au/news/electronic-cigarette-safety

Therapeutic Goods Administration – *Electronic Cigarettes*
https://www.tga.gov.au/community-qa/electronic-cigarettes

Western Australia Department of Health – *Electronic cigarettes (e-cigarettes)*
http://healthywa.wa.gov.au/Articles/A_E/Electronic-cigarettes-e-cigarettes

State and Territory Health Departments – *Contact Details*
http://www.health.gov.au/internet/main/publishing.nsf/Content/health-related.htm#state

Position statements

Australian Medical Association – *Tobacco Smoking and E-cigarettes (2015) – The AMA Position*
https://ama.com.au/position-statement/tobacco-smoking-and-e-cigarettes-2015

Cancer Council Australia and The Heart Foundation – *Joint Position Statement on Electronic Cigarettes*
http://wiki.cancer.org.au/policy/Position_statement_-_Electronic_cigarettes

Public Health Association of Australia – *Statement by the Public Health Associations of Australia on Electronic Cigarettes*
https://www.phaa.net.au/documents/item/704

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ANNUAL REVIEWS

Annual Review of Public Health

E-Cigarettes: Use, Effects on Smoking, Risks, and Policy Implications

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smoking initiation, smoking cessation, cancer, cardiovascular disease, lung disease

Abstract

Since e-cigarettes appeared in the mid-2000s, some practitioners, researchers, and policy makers have embraced them as a safer alternative to conventional cigarettes and an effective way to stop smoking. While e-cigarettes deliver lower levels of carcinogens than do conventional cigarettes, they still expose users to high levels of ultrafine particles and other toxins that may substantially increase cardiovascular and noncancer lung disease risks, which account for more than half of all smoking-caused deaths, at rates similar to conventional cigarettes. Moreover, rather than stimulating smokers to switch from conventional cigarettes to less dangerous e-cigarettes or quitting altogether, e-cigarettes are reducing smoking cessation rates and expanding the nicotine market by attracting youth.

INTRODUCTION

Cigarettes are a highly effective way of delivering the addictive drug nicotine. They do so by burning tobacco to create an aerosol of ultrafine particles that carries nicotine deep into the lungs, where it is rapidly absorbed, then travels through the left heart, reaching the brain in a few seconds. The combustion process also generates carcinogens, oxidizing agents, and other toxins. Like cigarettes, electronic cigarettes (e-cigarettes) create an inhaled aerosol of ultrafine particles that rapidly delivers nicotine to the brain. In contrast with cigarettes, however, e-cigarettes generate the aerosol by heating a liquid, usually consisting of propylene glycol or vegetable glycerin, nicotine, and flavoring agents, without any combustion (53).

Some in the health community, particularly in England, have embraced e-cigarettes as a safer alternative to conventional cigarettes and an effective way to stop smoking conventional cigarettes (85, 105) and have approved of their use by pregnant women (118). Despite the fact that a puff on an e-cigarette is almost certainly less toxic than a puff on a conventional cigarette, this optimistic scenario has not developed. Rather than encouraging smokers to switch from conventional cigarettes to less dangerous e-cigarettes or quitting altogether, e-cigarettes are reducing smoking cessation rates and expanding the nicotine market by attracting low-risk youth who would be unlikely to initiate nicotine use with conventional cigarettes.

TYPES OF E-CIGARETTES

E-cigarettes as originally marketed in 2004, known as cig-a-likes, were developed in China as a less dangerous alternative to conventional cigarettes (53). The early devices looked like a conventional cigarette, often including a small light on the tip that lit when the user puffed (**Table 1**). These

Table 1 Types of e-cigarettes. Reproduced under the terms of the CC-BY-NC-ND license, Reference 53

Product	Description	Some brands
Disposable e-cigarette 	Cigarette-shaped device consisting of a battery and a cartridge containing an atomizer to heat a solution (with or without nicotine). Not rechargeable or refillable and is intended to be discarded after product stops producing vapor. Sometimes called an e-hookah.	NJOY OneJoy, Aer Disposable, Flavorvapes
Rechargeable e-cigarette 	Cigarette-shaped device consisting of a battery that connects to an atomizer used to heat a solution typically containing nicotine. Often contains an element that regulates puff duration and/or how many puffs may be taken consecutively.	Blu, GreenSmoke, EonSmoke
Pen-style, medium-sized rechargeable e-cigarette 	Larger than a cigarette, often with a higher-capacity battery, may contain a prefilled cartridge or a refillable cartridge. Often come with a manual switch allowing the user to regulate length and frequency of puffs.	Vapor King Storm, Totally Wicked Tornado
Tank-style, large-sized rechargeable e-cigarette 	Much larger than a cigarette with a higher-capacity battery and typically contains a large, refillable cartridge. Often contains manual switches and a battery casing for customizing battery capacity. Can be easily modified.	Volcano Lavatube

early systems were generally inefficient at delivering nicotine, in part because the particle sizes of the aerosol were too large to penetrate deep into the lungs. Newer versions feature replaceable or refillable reservoirs and rechargeable batteries that generate smaller particles and more efficient nicotine delivery. These refillable systems allow users to separately purchase the e-cigarette liquid (known as e-liquid or e-juice) that contains varying levels of nicotine and comes in many different flavors (150). Running at a higher power (temperature) not only increases nicotine delivery, but also increases the amount of formaldehyde and other aldehydes that are naturally produced by heating up propylene glycol or vegetable glycerin (73, 98) and other toxins produced in the e-cigarette aerosol.

While some practitioners, researchers, and policy makers viewed e-cigarettes as a disruptive technology (122) that would compete with the established multinational cigarette company brands, by 2014 all the major multinational tobacco companies had entered the e-cigarette market. They did so either by buying existing e-cigarette companies (including Ruyan, the original Chinese e-cigarette company, which was bought by Imperial Tobacco) or by developing their own products (128). Indeed, as part of a larger policy to keep people using recreational nicotine rather than stopping tobacco use (8, 74), Philip Morris had developed the technology of the modern e-cigarette by the mid-1990s (38). As with their other alternative nicotine delivery systems, they chose not to take the product to market to avoid attracting the attention of the US Food and Drug Administration (FDA) and possibly triggering regulation of conventional cigarettes (8, 38). Although there continue to be independently owned "vape shops," from economic and political perspectives the e-cigarette business is now part of the traditional tobacco industry (33, 78).

WHY PEOPLE USE E-CIGARETTES

In the United States and many other countries, e-cigarettes are not subject to the same marketing and promotion restrictions that apply to cigarettes (136). As a result, e-cigarette companies are permitted to advertise on television and in mass media as well as through newer channels such as the Internet. US e-cigarette marketing expenditures increased from $3.6 million in 2010 to $125 million in 2014 (136), which translated into rapid increases in youth e-cigarette use (discussed below). Marketing messages echo well-established cigarette themes, including freedom, good taste, romance, sexuality, and sociability as well as messages claiming that e-cigarettes are healthy, are useful for smoking cessation, and can be used in smokefree environments. These messages are mirrored in the reasons that adults and youth cite for using e-cigarettes.

Adults

Adults cite predominantly three reasons for trying and using e-cigarettes: as an aid to smoking cessation, as a safer alternative to conventional cigarettes, and as a way to conveniently get around smokefree laws (99, 116, 131). Importantly, most adults who use e-cigarettes continue to smoke conventional cigarettes (referred to as dual users). In 2014 in the United States, 93% of e-cigarette users continued to smoke cigarettes (99), 83% in France (6), and 60% in the United Kingdom (131).

Youth

Although initial discussions within the health community about e-cigarettes focused on the potential for adults to use them as an alternative to cigarettes, youth have rapidly adopted them. In addition to the same three motivations that adults have cited for using e-cigarettes (52, 110), youth

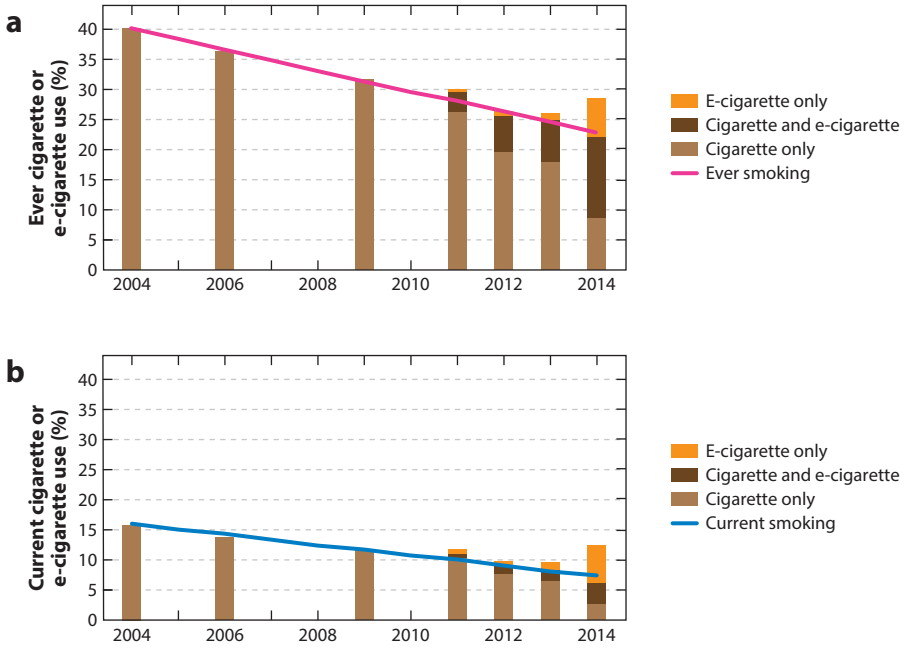

Figure 1

The advent of e-cigarettes did not affect declining trends in conventional cigarette smoking. After e-cigarettes became available, dual use of cigarettes and e-cigarettes increased, and some youth started using e-cigarettes alone; however, these changes did not affect the declining trend in cigarette use. This pattern was observed in both ever (≥1 puff lifetime; *panel a*) and current (use in past 30 days; *panel b*) cigarette use in the National Youth Tobacco Survey (NYTS), including dual use with e-cigarettes (cigarettes only, *light brown*; dual use, *dark brown*). E-cigarette-only users (*orange*) are at low risk of having initiated tobacco products with cigarettes (37). E-cigarette use was assessed starting in 2011. Adapted with permission from *Pediatrics* 2017 Volume 139, Issue 2, pii: e20162450. doi: 10.1542/peds.2016–2450, Copyright © 2017 by the American Academy of Pediatrics.

are attracted by e-cigarettes' novelty (52), the perception that they are harmless or less harmful than cigarettes (20, 52, 109, 110), and the thousands of flavors (5, 72, 136) (e.g., fruit, chocolate, peanut butter, bubble gum, gummy bear, among others).

As a result, youth e-cigarette use in the United States doubled or tripled every year between 2011 and 2014, and by 2014, e-cigarette use had surpassed conventional cigarette use in youth (36, 117). At the same time that e-cigarette use was increasing, cigarette smoking among youth declined (9, 68), leading some to suggest that e-cigarettes were replacing conventional cigarettes among youth (1, 80, 130) and are contributing to declines in youth smoking (84, 108, 111, 123). At least through 2014, however, e-cigarettes had no detectable effect on the decline in cigarette smoking among US adolescents (37) (**Figure 1**).

Whereas most of the youth who reported smoking cigarettes in the past 30 days (including dual users of cigarettes and e-cigarettes) in 2011–2014 have demographic and behavioral risk profiles (based on 2004–2009 data) consistent with smoking cigarettes, the risk profiles of the remaining e-cigarette-only users (about 25% of e-cigarette users) suggested that these individuals would have been unlikely to have initiated tobacco product use with cigarettes (37). These national results are consistent with regional US studies that also found that e-cigarette-only users display a lower risk profile than do cigarette smokers for smoking cigarettes (14, 24, 93, 143). Consistent with this

statement is that, in 2015, in the United States, 40% of 18–24-year-old current e-cigarette users had never smoked conventional cigarettes (27).

This rapid increase in e-cigarette-only use among youth and young adults is of concern because youth are more susceptible to developing nicotine dependence than are adults (136). In addition, nicotine has adverse effects on brain development, including to developing fetuses (41, 134, 136).

E-CIGARETTES AS A GATEWAY TO CIGARETTE SMOKING

A national cross-sectional study of Korean adolescents based on 2011 data was the first evidence that e-cigarette use was associated with higher cigarette use in youth (77). As with adults, dual use was the dominant pattern. The odds of being an e-cigarette user were 1.58 times [95% confidence interval (CI) 1.39–1.79] higher among students who had made an attempt to quit than for those who had not. It was rare for students who had formerly smoked but were no longer using cigarettes to be current e-cigarette users [odds ratio (OR) = 0.10; 95% CI 0.09–0.12]. A subsequent US cross-sectional study of data collected in 2011 and 2012 found similar results (35). As in Korea (77), current cigarette smokers who had ever used e-cigarettes were more likely to intend to quit smoking within the next year (OR = 1.53; 95% CI 1.03–2.28) but were less likely to have stopped smoking (OR = 0.24; 95% CI 0.21–0.28). The same US study also found that e-cigarette use was associated with progression from experimentation with cigarettes to established smoking. Among cigarette experimenters (youth who had smoked at least 1 puff of a cigarette), ever e-cigarette use was associated with higher odds of becoming an established smoker (smoking 100 cigarettes; OR = 6.31; 95% CI 5.39–7.39) and with current cigarette smoking (smoking 100 cigarettes plus smoking in the last 30 days; OR = 5.96; 95% CI 5.67–6.27).

Such cross-sectional data, however, do not allow investigators to draw causal conclusions because they represent a snapshot in time that does not reveal whether the e-cigarette or the conventional cigarette use came first. Reaching a causal conclusion requires longitudinal data where the same people are followed over time. As of February 2017, 9 longitudinal studies were quantifying the effect of starting tobacco use with e-cigarettes on progression to smoking conventional cigarettes (119). These studies all started with youth who had never smoked a cigarette, then compared subsequent smoking between youth who did and did not use e-cigarettes at baseline. Adjusting for demographic, psychosocial, and behavioral risk factors for cigarette smoking, the odds of subsequent cigarette smoking were quadrupled among e-cigarette users (**Figure 2**).

In sum, e-cigarettes are expanding the tobacco epidemic by bringing lower-risk youth into the market, many of whom then transition to smoking cigarettes. The 2015 US National Youth Tobacco Survey (117) suggests that this process may be starting. The small decline in smoking among middle-school students between 2014 and 2015 (2.5% to 2.3%) and the small increase in smoking among high school students (9.2% to 9.3%) are consistent with the observation that youth who initiated nicotine use with e-cigarettes (i.e., in 2014) are more likely to be smoking cigarettes a year later.

E-CIGARETTES AND SMOKING CESSATION

Determining how to assess the effects of e-cigarettes on smoking cessation has been one of the most contentious aspects of the debate over e-cigarette use. In contrast with nicotine replacement therapy, e-cigarettes are mass-marketed recreational consumer products; they are not medicine developed to be administered under clinical supervision. Another issue embedded in the debate over the assessment of e-cigarettes and smoking cessation is whether their effects should be assessed only among people who are actively using them as part of a smoking cessation attempt or on all

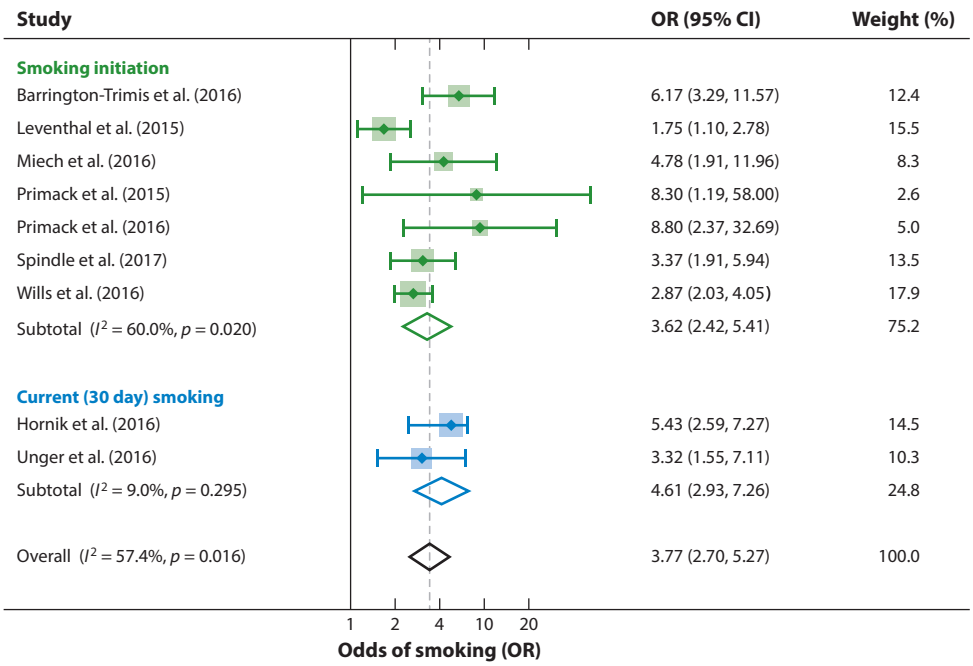

Figure 2

Ever e-cigarette use among never smokers at baseline quadruples the odds of being a smoker at follow-up. Meta-analysis is by the authors following Soneji et al. (119). Citations for studies: 15, 65, 79, 88, 102, 103, 121, 133, 142. Note: Weights are from random effects meta-analysis. Abbreviations: CI, confidence interval; OR, odds ratio.

smokers who use them regardless of motivation. This situation is further complicated because a major reason that smokers use e-cigarettes is to continue inhaling nicotine in locations where conventional cigarette smoking is prohibited (e.g., workplaces, public places such as restaurants and bars, and smokefree homes) (99, 116, 131). Smokefree environments both motivate and support quit attempts (43, 95, 144, 148). By potentially dulling the effects of smokefree environments, the real-world use of e-cigarettes could reduce quit attempts and keep people smoking. As more jurisdictions include e-cigarettes in their smokefree policies and people include them in voluntary smokefree home rules, this effect will likely be diminished.

As of June 2017, there was only one prospective randomized controlled trial of people using e-cigarettes to quit smoking (23). This trial, conducted in New Zealand, compared giving patients nicotine and non-nicotine e-cigarettes with giving them a voucher for nicotine replacement therapy (NRT) that they could redeem at a local pharmacy (usual care in New Zealand). There was no significant difference in efficacy compared with nicotine patches; both patches and e-cigarettes showed low efficacy. At 6 months, verified abstinence was 7.3% with nicotine e-cigarettes, 5.8% among those offered NRT, and 4.1% for those with non-nicotine e-cigarettes. However, because participants were handed the e-cigarettes and only given a voucher for NRT, these results likely overstated the efficacy of e-cigarettes and understated the efficacy of well-managed NRT. Another randomized trial (25) that compared nicotine and non-nicotine e-cigarettes found no consistent difference in smoking cessation. This study did not have a control group of smokers not using e-cigarettes, so it does not provide any information about the effects of e-cigarette use per se on smoking cessation.

These two studies (23, 25) have been the subject of four meta-analyses (40, 58, 71, 87), two from the Cochrane Collaborative (58, 87), which concluded, with low confidence, that nicotine e-cigarettes were associated with marginally more quitting than non-nicotine e-cigarettes. Another meta-analysis (107) pooled the data from these two trials, two cohorts, and two cross-sectional studies and reached the same conclusion. None of these meta-analyses drew conclusions about the efficacy of e-cigarettes versus other interventions for cessation because only one of the trials had a non-e-cigarette comparison (control) group (23).

Most research on the relationship between the use of e-cigarettes and quitting has been from observational studies that compare cigarette use among smokers who use e-cigarettes with smokers who do not use e-cigarettes. Although it does not support the same kind of causal conclusions that an experimental study (i.e., a randomized controlled trial) would, this approach has the advantage of quantifying the effects of e-cigarettes as actually used, including any indirect effects, such as discouraging cessation attempts. An analyses of 8 cohort observational studies suggested a possible reduction in quit rates with the use of e-cigarettes compared with no use of e-cigarettes (OR 0.74, 95% CI 0.55–1.00) (40).

Kalkhoran & Glantz (70) took a different approach, namely including all 20 available studies that reported a quantitative estimate of the association between e-cigarette use and having stopped smoking (2 clinical trials, 15 cohort studies, and 3 cross-sectional studies as of April 2015) and that had an appropriate control group (70). [They also presented a systematic review of all 38 available studies, regardless of whether they included the information necessary to estimate the effect of e-cigarette use on smoking cessation (70).] Odds of quitting cigarettes were 28% lower in those who used e-cigarettes compared with those who did not use e-cigarettes (OR 0.72, 95% CI 0.57–0.91). This conclusion did not significantly depend on differences in the study designs: studies of all smokers using e-cigarettes (irrespective of interest in quitting cigarettes) compared with studies of only smokers interested in cigarette cessation, study design, population, comparison group, control variables, time of exposure assessment, biochemical verification of abstinence, or definition of e-cigarette use. This result indicates that the overall conclusion that e-cigarettes are associated with less smoking cessation is not an artifact of the study design methods.

Between April 2015 and June 2017, seven more studies were published on the association between using e-cigarettes and quitting cigarettes (48, 62, 75, 81, 147, 149, 151). Updating the Kalkhoran & Glantz meta-analysis (70) to include these studies only slightly changed the pooled estimate of the effect (0.73, 95% CI 0.59–0.92) (**Figure 3**). The overall conclusion that smokers who used e-cigarettes were significantly less likely to stop smoking cigarettes remained.

Four studies (19, 63, 147, 151) did find significantly increased quitting among some e-cigarette users, suggesting that specific use patterns may be important. One study (19) found that intermittent e-cigarette users (more than once or twice but less than daily use) were less likely to quit smoking one year later than none-cigarette users, but those who had used e-cigarettes daily for at least one month were significantly more likely to quit cigarettes. Another study (63) found that all "cig-alike" users and nondaily tank system users had lower odds of quitting cigarettes, whereas daily tank system users were significantly more likely to quit. The third study (151) found that short-term e-cigarette use was not associated with a lower rate of smoking cessation, but long-term use was. The fourth study (147) found higher quitting smokers specifically using e-cigarettes as part of a quit attempt in countries with permissive e-cigarette policies (United States and United Kingdom) than those in countries with restrictive policies (Canada and Australia). In contrast, in the European Union (including Great Britain, specifically), a study of the relationship between e-cigarette use and having stopped smoking found less quitting among smokers who used e-cigarettes (75).

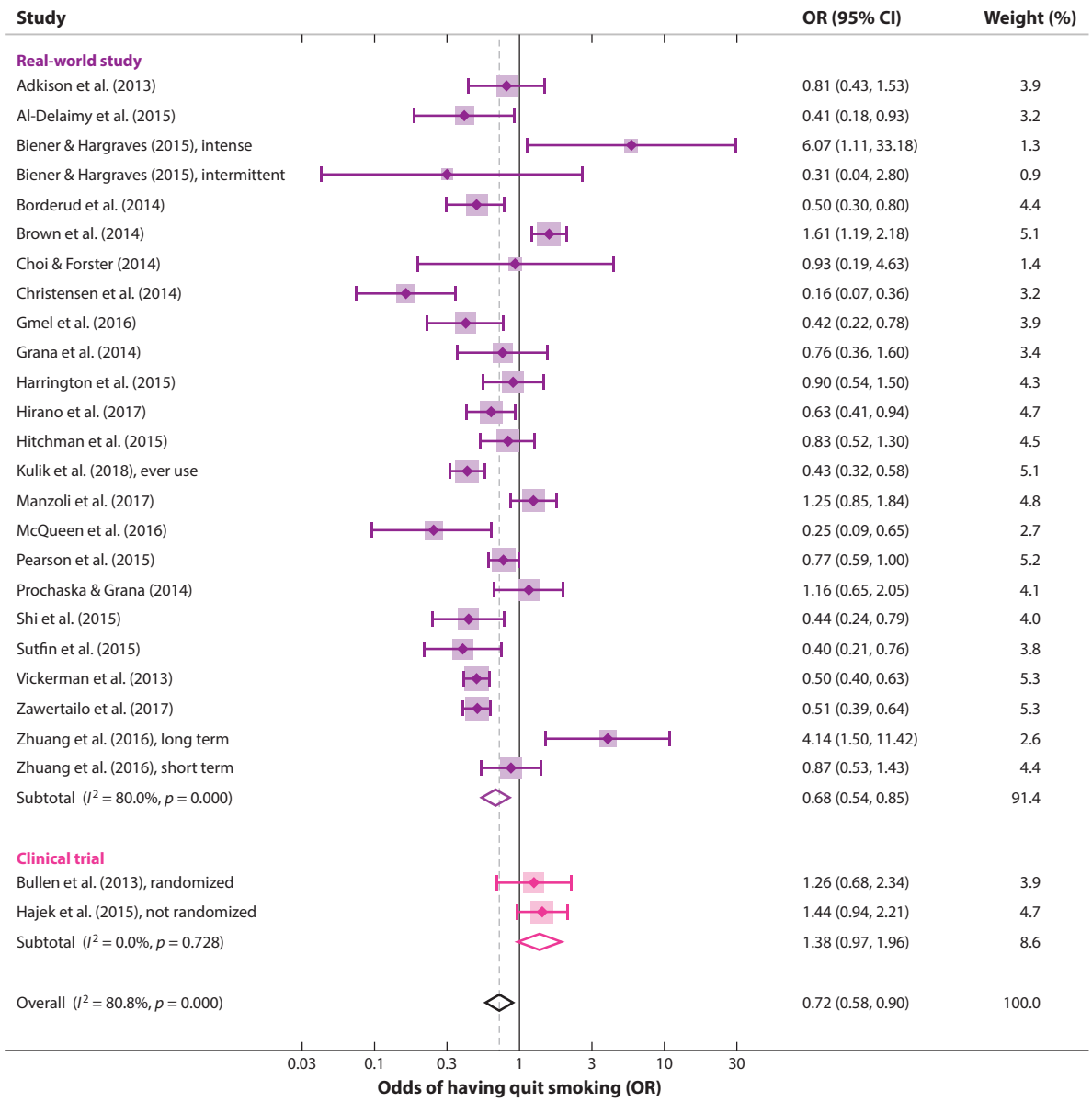

Figure 3

Smokers who use e-cigarettes are significantly less likely to have stopped smoking than smokers who do not use e-cigarettes, with the odds of quitting smoking depressed by 27%. Citations for studies: 2, 4, 19, 21, 22, 29, 30, 48, 54, 57, 62, 63, 75, 81, 86, 100, 104, 115, 124, 138, 147, 149, 151. Note: Weights are from random effects analysis. Abbreviations: CI, confidence interval; OR, odds ratio.

These results suggest that e-cigarettes are contributing to the tobacco epidemic by attracting smokers who are interested in quitting but reducing the likelihood of those smokers to quit successfully. This effect may be reflected in the fact that in 2015 the number of cigarettes consumed in the United States was higher than in 2014, the first time cigarette consumption increased since 1973 (139).

HEALTH EFFECTS OF E-CIGARETTES

Are "E-Cigarettes 95% Safer than Cigarettes"?

Influential health organizations in England, including Public Health England (85), the Royal College of Physicians (105), the Royal Society for Public Health (106), and the National Health Service (85, 96), have unequivocally stated that e-cigarettes are 95% safer than conventional cigarettes. This claim originated from a single consensus meeting of 12 people convened by D.J. Nutt in 2014 (97). They reached this conclusion without citing any specific evidence (32). The Nutt et al. paper did include this caveat: "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria" (97, p. 224), which has generally been ignored by those quoting this report (85, 96, 105, 106).

A 2015 editorial in *The Lancet* (39) identified financial conflicts of interest associated with Nutt et al. (97), noting that "there was no formal criterion for the recruitment of the experts." The Nutt et al. meeting was funded by Euroswiss Health and Lega Italiana Anti Fumo (LIAF). EuroSwiss Health is one of several companies registered at the same address in a village outside Geneva with the same chief executive, who was reported to have received funding from British American Tobacco (BAT) for writing a book on nicotine as a means of harm reduction (66) and who also endorsed BAT's public health credentials (127). Another of Nutt's coauthors, Riccardio Polosa, was Chief Scientific Advisor to LIAF, received funding from LIAF, and reported serving as a consultant to Arbi Group Srl, an e-cigarette distributor. He also received funding from Philip Morris International (84, 129). Later in 2015, the *BMJ* published an investigative report (51) that raised broader issues surrounding potential conflicts of interest between individuals involved in the Nutt et al. paper. *BMJ* provided an infographic illuminating undisclosed connections between key people involved in the paper and the tobacco and e-cigarette industries as well as links between the paper and Public Health England via one of the coauthors. Even so, as of June 2017, the "95% safer" figure remains widely quoted, despite the fact that evidence of the dangers of e-cigarette use has rapidly accumulated since 2014. This new evidence indicates that the true risk of e-cigarette use is much higher than the "95% safer" claim would indicate.

Cancer

Most discussion of the health effects of e-cigarettes has focused on cancer. As noted above, e-cigarettes deliver lower levels of carcinogens than do conventional cigarettes (50), and lower levels of carcinogens are found in the bodies of e-cigarette users than are found in smokers (114). While these observations suggest that e-cigarettes are likely less carcinogenic than conventional cigarettes, they do deliver carcinogens that can have effects at very low levels following repeat exposures (32). E-cigarettes deliver the tobacco-specific nitrosamine and potent lung carcinogen NNK [4-(N-methyl-N-nitrosoamino)-1-(3-pyridyl)-1-butanone, also known as nicotine-derived nitrosamine ketone] (50, 114). Some evidence indicates that the NNK dose-response curve for cancer is highly nonlinear, with substantial increases in risk at low doses (60). Known bladder carcinogens have been detected in the urine of e-cigarette users but not in nonusers (44). In addition, while nicotine is not a carcinogen, it does promote the growth of blood vessels that supply tumors and it speeds tumor growth (59).

The fact is, however, cardiovascular and noncancer lung disease kill more smokers (135) than does cancer (**Figure 4**), which makes it important to assess the impact of e-cigarette use on these other diseases.

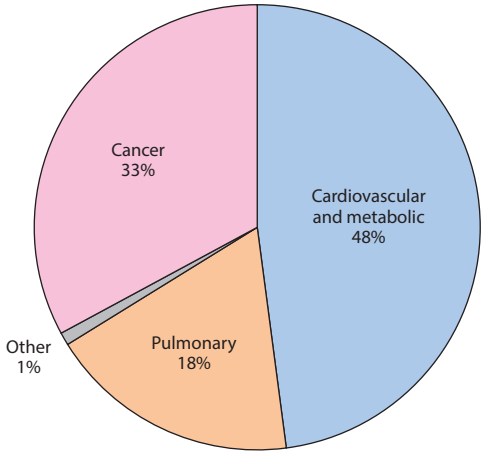

Figure 4

Between 1965 and 2015, active and passive smoking killed 21 million people. Although most discussion of smoking and disease focuses on cancer, cardiovascular disease and metabolic and noncancer pulmonary disease kill most smokers (134).

Cardiovascular Disease

E-cigarettes adversely impact the cardiovascular system (17, 113). Although the specific role of nicotine in cardiovascular disease remains debated (16, 17), nicotine is not the only biologically active component in e-cigarette aerosol. As noted above, e-cigarettes work by creating an aerosol of ultrafine particles to carry nicotine deep into the lungs. These particles are as small as—and sometimes smaller than—those in conventional cigarettes (45) (**Figure 5**). These ultrafine particles are themselves biologically active, trigger inflammatory processes, and are directly implicated in causing cardiovascular disease and acute cardiovascular events (101). The dose-response effect for exposure to particles is nonlinear, with substantial increases in cardiovascular risk with even low levels of exposure to ultrafine particles (101). For example, exposure to secondhand cigarette smoke has nearly as large an effect on many risk factors for cardiovascular disease and the risk of

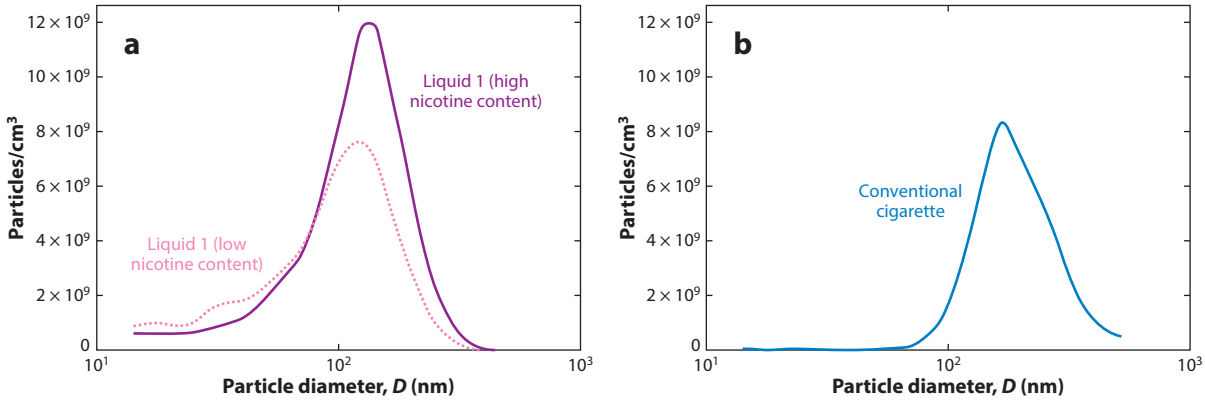

Figure 5

Particle number distribution from (*a*) mainstream aerosol in e-liquid 1 and from (*b*) conventional cigarette as a function particle size (diameter, *D*). Adapted from Fuoco et al. (45) with permission from the publisher. Copyright © 2013 Elsevier Ltd.

acute myocardial infarction as does being an active smoker (13). In addition, e-cigarettes expose users to acrolein and other aldehydes (17, 18). Like conventional cigarette smokers, e-cigarette users experience increased oxidative stress (26, 92) and increases in the release of inflammatory mediators (26, 61). E-cigarette aerosol also induces platelet activation, aggregation, and adhesion (64). All these changes are associated with an increased risk of cardiovascular disease.

These physiological changes are manifest in rapid deterioration of vascular function following use of e-cigarettes. E-cigarette and traditional cigarette smoking in healthy individuals with no known cardiovascular disease exhibit similar inhibition of the ability of arteries to dilate in response to the need for more blood flow (26). This change reflects damage to the lining of the arteries (the vascular endothelium), which increases both the risk of long-term heart disease and an acute event such as a myocardial infarction (heart attack) (141, 145, 146). Using e-cigarettes is also accompanied by a shift in balance of the autonomic (reflex) nervous system toward sympathetic predominance (26, 92), which is also associated with increased cardiac risk (56, 126).

The biological stresses that e-cigarette use impose on the cardiovascular system are manifest as an increase in risk of acute myocardial infarction (125). A cross-sectional analysis of data in the US 2014 and 2016 National Health Interview Surveys revealed that daily e-cigarette use was associated with increased odds of having suffered a myocardial infarction (OR = 1.79, 95% CI 1.20–2.66; $p = 0.004$), controlling for conventional cigarette smoking, demographic characteristics (age, gender, body mass index, family income) and health characteristics (hypertension, diabetes, and hypercholesterolemia) (125). Significantly, the effect of using e-cigarettes on the odds of myocardial infarction approached what was found with conventional cigarette smoking (OR = 2.72, 2.29–3.24; $p < 0.001$) (125).

Lung Disease

As with cardiovascular disease, evidence consistently indicates that exposure to e-cigarette aerosol has adverse effects on lungs and pulmonary function (31, 91). Repeated exposure to acrolein, which is produced by heating the propylene glycol and glycerin in e-liquids, causes chronic pulmonary inflammation, reduction of host defense, neutrophil inflammation, mucus hypersecretion, and protease-mediated lung tissue damage, which are linked to the development of chronic obstructive pulmonary disease (94). E-cigarette aerosol also exposes users to highly oxidizing free radicals (49). Animal studies have also shown that e-cigarettes increase pulmonary inflammation and oxidative stress while inhibiting the immune system (31).

Consistent with these experimental results, people who used e-cigarettes experienced decreased expression of immune-related genes in their nasal cavities, with more genes suppressed than among cigarette smokers, indicating immune suppression in the nasal mucosa (82). E-cigarette use upregulates expression of platelet-activating factor receptor (PAFR) in users' nasal epithelial cells (90); PAFR is an important molecule involved in the ability of *S. pneumoniae*, the leading cause of bacterial pneumonia, to attach to cells it infects (adherence). In light of the immunosuppressive effects observed in nasal mucosa (82), there is concern that e-cigarette use will predispose users toward more severe respiratory infections, as has been demonstrated in mouse studies (67).

Given these effects, it is not surprising that e-cigarette use is associated with a doubling of the risk of symptoms of chronic bronchitis among US high school juniors and seniors (OR = 2.02, 95% CI 1.42–2.88) with higher risk associated with higher use; these risks persisted among former users (83). Similarly, current e-cigarette use was associated with an increased diagnosis of asthma among Korean high school students (adjusted OR = 2.74, 95% CI 1.30–5.78 among current e-cigarette users who were never cigarette smokers) (28). E-cigarette users were also more likely to have had days absent from school due to severe asthma symptoms.

Summary of Health Effects

Although e-cigarettes deliver lower levels of carcinogens than do conventional cigarettes, and therefore may pose less cancer risk to users (albeit not zero cancer risk), they still expose users to high levels of ultrafine particles and other toxins that may substantially increase cardiovascular and noncancer lung disease risk. The similarities between the effects of e-cigarettes and those of conventional cigarettes on determinants of cardiovascular and lung disease make it likely that e-cigarettes will impose similar long-term cardiovascular and pulmonary risks as those associated with conventional cigarettes. Cardiovascular and noncancer pulmonary diseases account for about two-thirds of smokers' premature deaths from tobacco-induced diseases (**Figure 4**), so it would not be surprising if e-cigarettes impose half (or more) of the overall long-term risks as those from conventional cigarettes.

USE OF E-CIGARETTES IN SMOKEFREE ENVIRONMENTS

Using e-cigarettes in places where smoking is prohibited (e.g., workplaces, public places such as restaurants and bars, and otherwise smokefree homes) is one of the reasons that people use e-cigarettes (99, 116, 131). (This situation is changing as more places include e-cigarettes in their smokefree policies.) Even though e-cigarettes do not produce any sidestream smoke (the smoke that comes off the lit end of a smoldering cigarette), they do pollute the air in the form of exhaled mainstream aerosol from people using e-cigarettes. Nicotine, ultrafine particles, and products of heating propylene glycol and glycerin are increased in the air where e-cigarettes are being used, although, as expected, at lower levels than produced by smoking the same number of conventional cigarettes (12, 34, 46, 112).

As with conventional cigarettes, however, when several people are using e-cigarettes indoors at the same time, the air can become polluted. For example, levels of fine particulate matter ($PM_{2.5}$) in a large hotel event room (4,023 m^3) increased from 2–3 $\mu g/m^3$ to as high as 819 $\mu g/m^3$ interquartile range: 761–975 $\mu g/m^3$) when 59–86 people were using e-cigarettes (120). This level is comparable to a very (conventional tobacco) smoky bar or casino and dramatically exceeds the US Environmental Protection Agency annual time-weighted standard for $PM_{2.5}$ of 12 $\mu g/m^3$ (137).

Evidence has also shown that bystanders absorb nicotine when people around them use e-cigarettes at levels comparable with exposure to conventional cigarette secondhand smoke (12). In a study of nonsmokers living with nicotine e-cigarette users, those living with conventional cigarette smokers, or those living in homes where no one used either product, cotinine (a metabolite of nicotine) levels in bystanders' urine were significantly elevated in both the people exposed to secondhand e-cigarette aerosol and those exposed to secondhand tobacco smoke compared with people living in aerosol- and smoker-free homes. Interestingly, the levels of elevated urinary cotinine in the two exposed groups were not significantly different (although the passive smokers had higher point estimates), despite the fact that the increase in air pollution in the smokers' homes was much higher than in the e-cigarette users' homes (geometric mean air nicotine concentrations of 0.13 $\mu g/m^3$ in e-cigarette users' homes, 0.74 $\mu g/m^3$ in smokers' homes, and 0.02 $\mu g/m^3$ in the control homes).

On the basis of emerging evidence, in 2014 the American Industrial Hygiene Association (3, p. 2) concluded that "e-cigarettes are not emission-free and that their pollutants could be of health concern for users and those who are exposed secondhand. . . .[T]heir use in the indoor environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants."

Similarly, in 2016 the American Society of Heating, Refrigeration and Air-Conditioning Engineers (ASHRAE) updated its standard for "Ventilation for Acceptable Indoor Air Quality" to incorporate emissions from e-cigarettes into the definition of "environmental tobacco smoke," which is incompatible with acceptable indoor air quality (10, 11). As of April 2017, 12 US states and 615 localities had prohibited the use of e-cigarettes in venues in which conventional cigarette smoking was prohibited (7).

POLICY ISSUES

Initial hopes that e-cigarettes would be both a less toxic competitor to conventional cigarettes and a help to people who attempt to quit smoking cigarettes (76) have not translated into real-world positive effects. Instead, e-cigarettes have simply become another class of tobacco products that are maintaining and expanding the tobacco epidemic.

As the major tobacco companies have moved into, and increasingly dominated, the e-cigarette market, they are dominating the political and policy-making environments just as they have in conventional cigarette policy making (33, 78). As they have done to influence tobacco control policies for conventional cigarettes (132), the large companies often try to stay out of sight and work through third parties that can obscure their links to the tobacco industry (33). The one difference from the historical pattern of industry efforts to shape tobacco policy from behind the scenes is that there are also genuine independent sellers of e-cigarettes and associated users (so-called vape shops) who are not necessarily being directed by the cigarette companies. These smaller operators are, however, losing market share to the big tobacco companies (89), and the real political power is now being exercised by the cigarette companies. The cigarette companies try to take advantage of the existence of independent players while acting through the industry's traditional allies and front groups (33, 42).

Countries have reacted in a variety of ways to the introduction of e-cigarettes in their markets, ranging from no regulations to a ban on e-cigarettes. The Conference of the Parties to the World Health Organization Framework Convention (which does not include the United States) has generally taken a cautious approach to e-cigarettes (140) and has agreed that regulatory measures need to be implemented to, at a minimum, ensure that e-cigarettes do not worsen the tobacco epidemic (140). Because of these realities, e-cigarettes should be integrated into tobacco control policies at all levels of government.

To minimize deleterious health effects, we recommend the following measures:

- Prohibit the use of e-cigarettes anywhere that use of conventional cigarettes is prohibited, including in smokefree homes;
- Tax e-cigarettes at levels comparable to cigarettes;
- Include e-cigarettes in public education campaigns, particularly communicating the facts that they are not "harmless water vapor," do pollute the air, are a gateway to conventional cigarettes, and are increasingly sold by the same multinational companies that sell conventional cigarettes;
- Prohibit the sale of e-cigarettes to anyone who cannot legally buy cigarettes or in any venues where the sale of conventional cigarettes is prohibited;
- Establish a minimum purchase age of 21;
- Subject e-cigarettes to the same marketing restrictions that apply to conventional cigarettes (including no television, radio, or outdoor advertising);
- Prohibit cobranding of e-cigarettes with cigarettes or marketing in a way that promotes dual use;
- Prohibit flavored e-cigarettes, particularly menthol, candy, fruit, and alcohol flavors;

- Prohibit claims that e-cigarettes are effective smoking cessation aids until e-cigarette companies provide sufficient evidence that, as actually used in the real world, e-cigarettes are effective for smoking cessation;
- Prohibit any health claims about e-cigarette products until and unless they are authorized by the appropriate regulatory agencies (the FDA in the United States) using scientific and regulatory standards that account for dual use and effects of e-cigarette use on depressing smoking cessation; and
- Establish quality standards for ingredients and functioning of e-cigarette devices.

Implementing these policies would reduce the likelihood that e-cigarettes will continue to expand and extend the tobacco epidemic.

THE FUTURE

Because e-cigarettes have been on the market for only a few years, the long-term population health effects are not known. Nevertheless, it is already clear that e-cigarettes are prolonging and extending the tobacco epidemic by reducing smoking cessation and expanding the tobacco market by attracting youth who would otherwise be unlikely to initiate tobacco use with conventional cigarettes. On the basis of the short-term effects that have been identified to date, e-cigarettes likely have cardiovascular and noncancer lung disease risks similar to those associated with smoking conventional cigarettes. Under most reasonable alternative use pattern scenarios, this is a high enough risk to lead to a net population harm even if some smokers switch to e-cigarettes (47, 69, 80). To minimize harm, e-cigarettes as well as the timing and location of their promotion and use should be regulated like other tobacco products.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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Submission to The Standing Committee on Health, Aged Care and Sport on Electronic Cigarettes and Vapourisers.

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Professor Simon Chapman AO PhD FASSA Hon FFPH (UK) is an Emeritus Professor in Public Health at the University of Sydney, from which he retired in February 2016. He has authored 515 articles, editorials and letters published in peer reviewed journals and 20 books and major reports. His work has been cited over 12,000 times. In 1997 he won the World Health Organisation's World No Tobacco Day Medal and in 2003 he was awarded the American Cancer Society's Luther Terry Award for outstanding individual leadership in tobacco control. In 2008 he won the NSW Premier's Cancer Researcher of the Year award and the Public Health Association of Australia's Sidney Sax medal. He was inaugural deputy editor (1992-1997) then editor (1998-2008) of the BMJ's specialist journal *Tobacco Control.* He is now its editor emeritus. In 2013, he was made Australian Skeptic of the Year and an Officer in the Order of Australia for his contributions to public health.

Professor Mike Daube AO has been Professor of Health Policy at Curtin University since 2005. Before this he was Director General of Health for Western Australia. His roles have included President of the Public Health Association of Australia, President of the Australian Council on Smoking and Health, Deputy Chair of the National Preventative Health Taskforce (and chair of the tobacco committee), Vice-Chair of the WHO FCTC Review Group, and chair, member and patron of many further government and non-government committees in Australia and elsewhere. He has worked on tobacco issues nationally and internationally for more than forty years, and has published widely on this and related issues. He is an Officer in the Order of Australia, and has received further awards from the World Health Organization, the American Cancer Society's Luther Terry Distinguished Career Award, the Australian Medical Association, the National Heart Foundation of Australia, the Public Health Association of Australia, the Thoracic Society of Australia and New Zealand, Environmental Health Australia, the World Federation of Public Health Associations and many other organisations.

David Bareham MSc has been working as a Specialist Respiratory Physiotherapist at Lincolnshire Community Health Services UK NHS Trust for ten years. He currently has two peer reviewed articles related to electronic cigarettes, including one with *Lancet Respiratory Medicine*. He has another review article on e-cigarettes which has just been accepted for publication in the U.S. Last October, in collaboration with Professor Martin McKee and Professor Simon Capewell, he presented Expert Testimony to the English National Institute for Health and Care Excellence Public Health Advisory Committee on the Role of E-cigarettes in Smoking Cessation. His opinions here are his own, and not necessarily those of his employer.

Associate Professor Matthew Peters MD FRACP FThorSoc is a Respiratory Physician and Head of Respiratory Medicine at Concord Hospital. He has academic appointments at Macquarie University and Sydney University. Although a full-time clinician, he has authored over 100 peer-reviewed publications and he has supervised 10 successful PhD students. For more than a decade he was Chair of Action on Smoking and Health, Australia. In 2017 his work in preventing and improving the treatment and care of patients with lung cancer was acknowledged when he received a lifetime achievement award from Lung Foundation Australia.

Summary

The Therapeutic Goods Administration is in every sense Australia's national "umpire" on claims about therapeutic product safety and efficacy. Its decisions over decades have given Australia one of the world's best and most envied therapeutic regulatory systems. Those who have been working to have the TGA circumvented as this umpire are challenging its authority on the flimsiest of pretexts. They have refused to accept the TGA umpire's decision, a course of action which brings them great discredit.

Given current knowledge of risk and uncertainty of benefit for ENDS, unregulated availability should not be an option. The purported benefits are small, uncertain and certainly unexceptional. However, evidence of harms are emerging.

As a core part of the case being put forward for the benefits of ENDS is based on a therapeutic claim (efficacy in smoking cessation), the TGA remains the appropriate regulator for nicotine-containing products. The TGA is also vastly experienced in assessing therapeutic product safety. For these two reasons ENDS must remain under TGA regulation.

To date, there is poor evidence of cessation superiority compared to best practice. Where an effect has been shown it has been small in magnitude. As concluded by the Cochrane Collaboration, the available data on ENDS' efficacy in smoking cessation are low to very low in quality. The clearest conclusion is that there is no exceptional scientifically identified effect that would justify any exceptionalist departure from normal TGA regulatory processes. In addition, the available data apply to only a small number of device/delivery system/delivery parameter possibilities among the plethora available (and increasing in number). Lastly, it is important to consider that smoking cessation is the reason for use of ENDS in a declining minority of users (Ayers, 2017). Most users have no intent to quit smoking, but to only cut down in the false belief that reduced smoking is harm reducing. Because dual users (smoking plus ENDS) do not reduce their risk of harm, the majority of users therefore will not derive even any of the health benefits postulated.

The failure of governments in nearly every nation to regulate tobacco *the product* (advertising, packaging, misleading claims and smoke free areas are all strongly regulated) is not a sensible reason for removing ENDS from TGA regulation. To remove nicotine regulation from the TGA would be to learn nothing from the historic failure to regulate cigarettes. The argument being made by those urging this to happen is "cigarettes are an unregulated public health disaster and are freely available. Let's now take the same unregulated route with ENDS."

Other than injuries caused by exploding ENDS, the harms that may arise from their long term use are unlikely to manifest in the short term. This was of course the history of emerging knowledge about the harms of smoking. Anyone proposing that cigarette smoking was apparently safe 10 years after mass use commenced would have been revealed to have been very badly wrong. ENDS advocates make such parallel claims today. These may turn out to be true or to be recklessly irresponsible - all the more reason to defer to the TGA.

The TGA's regulatory assessment and scheduling powers will allow it to assess submissions for ENDS approval and to then calibrate scheduling that may be either strengthened or liberalised as evidence of harms and/or benefits emerge. Such flexibility is routine in the TGA and occurred (for example) with nicotine replacement therapy which was earlier a prescription only item and is now available in low doses over the counter.

Key questions for policy makers include:

- What is the net impact of the widespread use of ENDS?
- What might be the health effects of long term vaping?
- Does the proliferation in ENDS use tip more people permanently out of smoking than it holds in smoking because of widespread erroneous beliefs that cutting down cigarettes is harm reducing enough?
- Does it pull significant numbers of ex-smokers back into nicotine dependency?
- Does it see children and young people who may have never used any form of nicotine product start vaping or encouraged to think of vaping or smoking as normal and acceptable behaviour for them?

While some nations impose a ban on ENDS, the focus of this submission is on the case for regulating their content and availability through the established processes of the TGA

Note: Throughout, we use the acronym ENDS (Electronic Nicotine Delivery Systems) to refer to electronic cigarettes and all other vapourising systems used to vapourise nicotine and all other materials that are inhaled by their users.

We have arranged the material in our submission sequentially to address the Committee's Terms of Reference. Under each we have set out frequently asked questions often posed in the ENDS debate, and then addressed these. Appendices 1,2 and 4 are found at the end of this document. Appendix 3 is separately attached.
A study of smokers in 18 European nations published in *Preventive Medicine* [Fernandez et al, 2015] provides important data of direct relevance to the hardening hypothesis.

The most recognised way of measuring the "hardness" of smoking is the Heaviness of Smoking Index (HSI). This scores smokers out of a maximum of six, comprising a score of one to three for number of cigarettes smoked each day, and one to three on the time taken to lighting up the first cigarette of the day.

The European study, involving 5,136 smokers drawn from a total 18-country sample of more than 18,000 people, found that across the 18 nations, there was no statistically significant relationship between a nation's smoking prevalence and the HSI.

If the hardening hypothesis was correct, nations with low smoking prevalence would have had higher HSI scores in the remaining smokers. They would have been smoking more cigarettes and lighting up earlier in the morning in nations with low smoking prevalence than in those with high. But they were not.

Similar findings have been reported for the United States. Data on smoking in 50 US states for 2006–2007 indicate that the mean number of cigarettes smoked daily, the percentage of cigarette smokers who smoke within 30 minutes of waking, and the percentage who smoke daily were all significantly lower in US states with low smoking prevalence (see http://www.bridgingthegapresearch.org/_asset/vgm11t/Giovino_2009_TobaccoChartbook.pdf) . Again, this provides compelling evidence against the hardening hypothesis.

In Australia, a 2012 paper [Matthews, Hall & Gartner, 2010] examined three series of Australian surveys of smoking – the National Drug Strategy Household Survey (NDSHS), National Health Survey (NHS) and National Survey of Mental Health and Well-being (NSMHW) – that spanned seven to ten years.

The authors found that in two of the surveys (NDSHS and NHS), while smoking fell across the population, there was no change in the proportion of smokers who smoked less than daily, while in the NSMHW survey, that proportion increased from 6.9% in 1997 to 17.4% in 2007 (indicating a softening, not a hardening of smoking).

The authors concluded that the evidence presented:

> "weak evidence that the population of Australian smokers hardened as smoking prevalence declined."

Undeterred by this evidence, advocates for vaping centre their arguments around assumptions that there are many smokers who they claim are "unable" or "unwilling" to quit smoking. These are both very fluid and imprecise constructs.

Hundreds of millions have quit smoking

It is important to note that many hundreds of millions of smokers have quit smoking all over the world in the years before and since the evidence about the harms of smoking first began being publicised. Many very heavy smokers were among this population.

Most ex-smokers (between two-thirds and three-quarters) quit unassisted (i.e. without using any form of medication, nicotine replacement or getting professional assistance of any sort). [Chapman & McKenzie, 2010]. It is important to recall that nicotine replacement therapy (NRT) only became available in the early 1980s. Before that, a huge number of smokers stopped smoking permanently. [Smith & Chapman, 2014]. Those who stopped smoking without using NRT were not just light, non-addicted smokers but included many heavy and strongly addicted smokers.

In 1955, five years after Ernst Wynder and Evarts Graham's historic study of smokers and lung cancer was published in JAMA (see http://www.epidemiology.ch/history/PDF%20bg/Wynder%20and%20Graham%201950%20tobacco%20smoking%20as%20a%20possible%20etiologic.pdf) 7.7 million Americans (6.4% of the population) were former smokers. Ten years later, following widespread publicity surrounding the 1964 US Surgeon General's Report, this had ballooned to 19.2 million (13.5%) ex-smokers.

By 1975, 32.6 million Americans (19.4%) had stopped smoking.

In 1978, the then director of the US Office in Smoking and Health noted in a National Institute of Drug Abuse Monograph, "In the past 15 years, 30 million smokers have quit the habit, *almost all of them on their own*." (our emphasis) Many of these quitters had been very heavy smokers.

Today, quitting unaided (going "cold turkey") remains the most common way that most ex-smokers have quit, despite more than 20 years of the availability and heavy promotion of nicotine-replacement therapy and other drugs and many other promoted methods of quitting both before and since. One should be very circumspect about voices trying to downplay this major and enduring phenomenon and promoting the view that stopping smoking requires pharmacological or professional help.

"Unable" to stop?

The "unable" to quit group are said to be those who want to stop smoking, but who have tried many times unsuccessfully and are now described by some as "unable" to stop smoking. It is certainly correct that some smokers find it very hard to stop smoking. But it

is equally the case that there are very many ex-smokers who after a succession of failed attempts to stop, then succeed. Indeed, many smokers who quit do so after a number of previous attempts. Such people therefore cannot be described as being "unable" to stop. They might better be described as being those who found it difficult to stop, to varying degrees.

Many quit attempts are clearly not serious attempts to stop, much in the same way that many *attempts* to get fit, lose weight, drink less and so on are also not serious attempts. Research has shown that many smokers who have had few thoughts about quitting make spontaneous quit attempts, and that such attempts are more successful than planned attempts [West & Sohal, 2006; Resnicow et al 2014J

Any roles that ENDS play in assisting some who find it difficult to quit are a far different proposition than than that driving much vaping marketing which is to encourage as many smokers as possible to switch to ENDS. This would include many who may never have any serious difficulty in quitting.

Public policy on ENDS' role in cessation needs to consider how best to make any ENDS products that have been approved for safety and quality accessible to smokers genuinely in need of this form of assistance, without risking the proliferation of these nicotine delivery devices to those who are likely to be able to quit anyway, to those who have no intention of quitting, and to non-smokers (especially children and young people).

Most smokers want to quit, and messaging from vaping interests that they should instead vape (and perhaps merely *reduce* their smoking) is a message that can seriously threaten the 50 year historical momentum for smokers to quit which has seen smoking rates in Australia fall almost continuously since 1980. This of course, would be an outcome that would be very welcomed by the tobacco industry, in which all major companies have bought into the ENDS industry. (see http://vaping360.com/the-battle-for-the-electronic-cigarette-market/)

In this respect, a core message of ENDS marketing is little different to those promoted over many years by tobacco companies during the many years of the low tar fraud, encapsulated by an infamous promotion for an earlier alleged harm reduced tobacco product, the US cigarette brand *True* (see below).

The "unwilling" to stop group

The "unwilling" group are often said to be those who enjoy smoking , or who have no interest or intention of stopping. However, ENDS advocates claim that many in this group have a strong interest in discontinuing smoking (overwhelmingly because of their awareness of the harms of smoking that have been so effectively communicated by tobacco control campaigns, pack warnings and doctor-patient advice) but want to maintain their nicotine addiction through vaping. They believe (or hope) that vaping is far less dangerous than continuing to smoke (see the next term of reference below) and that nicotine is virtually benign in the exposures received by smokers or vapers (also see term of reference #2 for comments on this point).

While some 90% of smokers regret that they ever started to smoke [Fong et al, 2004] some smokers claim that they "enjoy" smoking. A large part of the "enjoyment" that smokers get from smoking is the very palpable experience of relief that smokers get when the nicotine receptors in their brains are replenished with a dose of nicotine. When nicotine dependent smokers go without nicotine they can experience distressing symptoms - "cravings" - which are rapidly relieved by nicotine.

In this way, the ”pleasure” of smoking is in large part the pleasure of avoiding the distress caused by the absence of nicotine in one's body. To refer to this as “pleasure” is like arguing that being beaten up every day is something you want to continue with, because it feels so good when the beating stops for a while. And clearly hundreds of millions of ex-smokers who experienced this “pleasure” decided that the risks it brought far out-weighed the benefits of continuing.

What is the quality of the evidence to date about ENDS assisting smokers to quit smoking?

In assessing evidence about any intervention in smoking cessation, a variety of evidence can be considered.

Randomised Controlled Trials

Those who research the quality of evidence refer to high and low quality evidence. The highest quality evidence that can be considered in answering the question of whether vapourisers are useful in smoking cessation is the randomised controlled trial (RCT). This is where smokers wanting to quit smoking would be randomised into several different study groups. Typically, these would be where some would be allocated to use nicotine containing vapourisers; some given another form of smoking cessation intervention (such as NRT or varenicline); and others would be given a non-nicotine vaporiser (placebo).

At the time of writing (June 2017), there is only one recognised RCT that reasonably complies with these basic methodological characteristics [Bullen et al, 2013]. As the authors stated:

> “657 people were randomised (289 to nicotine e-cigarettes, 295 to patches, and 73 to placebo e-cigarettes) . . .” At 6 months, verified (biochemically confirmed) abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and 4.1% (three of 73) with placebo e-cigarettes (risk difference with nicotine e-cigarette vs patches 1.51 [95% CI -2.49 – 5.51]; for nicotine e-cigarettes vs placebo e-cigarettes 3.16 [95% CI -2.29 – 8.61]). Achievement of abstinence was substantially lower than we anticipated for the power calculation, thus we had insufficient statistical power to conclude superiority of nicotine e-cigarettes to patches or to placebo e-cigarettes.”

Other significant methodological concerns with this trial included that the delivery of nicotine e-cigarettes to participants was, unrealistically, via courier, whereas the patches group had to take a voucher to a chemist in order to obtain their nicotine replacement

therapy. Perhaps unsurprisingly, there was a high loss-to-follow-up noted in the patches group. It is entirely feasible, therefore, that the study *overestimated* the very "modest" effect size of nicotine e-cigarettes, and *underestimated* the effect size of well-managed nicotine replacement therapy.

Another RCT assessing the efficacy of ENDS for smoking cessation (Caponnetto et al, 2013) involved a study of smokers, though, in contrast to the aforementioned RCT study, *not* seeking to quit smoking. It involved only placebo comparison groups, and found no consistent differences in smoking cessation between nicotine e-cigarette and placebo e-cigarette.

In September 2016, the Cochrane Collaboration published an updated review and meta-analysis of this evidence, and the usefulness of electronic cigarettes in smoking cessation. It concluded:

> "There is evidence from two trials that ECs help smokers to stop smoking in the long term compared with placebo ECs. However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low' by GRADE standards. The lack of difference between the effect of ECs compared with nicotine patches found in one trial is uncertain for similar reasons." (Cochrane Collaboration Hartmann-Boyce et al, 2016)

However, in contrast to this analysis demonstrating, at best, a very weak positive association between e-cigarette use and smokers stopping smoking, another meta-analysis of the current RCT data [El Dib et al, 2017], identifying the aforementioned high loss-to-follow-up issue, highlighted that another entirely feasible interpretation ("plausible worse case sensitivity analysis") is that e-cigarettes "fail to show a difference" in smoking cessation compared to placebo. As they point out:

> ". . . the 95% CI of the relative risk crossed 1.0 and a plausible worse case sensitivity analysis to assess the risks of bias associated with missing participant data yielded results that were inconsistent with the primary complete case analysis."

We understand that several RCTs are now under way. These should be important in increasing knowledge about ENDS' efficacy in cessation.

Cohort studies on cessation

A lower form of evidence than RCTs is the longitudinal cohort study. This is where a group of smokers are followed for a long period to determine what proportions using different methods of trying to quit are not smoking at different times of follow-up. Because of the

very common phenomenon of relapse in smoking cessation, studies which report long follow-up data are more important than those reporting short-term findings,

The aforementioned Cochrane Review did not apply meta-analysis to cohort data on ENDS. However, the El Dib review did (n=8 studies), and in fact noted a potential *suppression* of chances in successful quitting when people use ENDS: "Cohort studies provide very low-certainty evidence suggesting a possible reduction in quit rates with use of ENDS compared with no use of ENDS" [El Dib, 2017].

Cross-sectional studies

Cross-sectional studies are a still lower form of evidence. These are where "snapshot" surveys of the community are undertaken and data obtained on the proportion of smokers who answer that they are no longer smoking.

Weaknesses in relying on this type of data include, fundamentally (as any epidemiology 1 student knows) that causality can never be claimed from cross sectional studies. Because data from participants in a cross-sectional (snapshot) studies are recorded only once, inference of temporal associations between ENDS use and smoking outcomes cannot be made. Only associations, not causation can be inferred from cross sectional studies.

An example of cross-sectional data from which inappropriate claims *were* made about e-cigarette cessation effects was a secondary analysis of the 2014 Eurobarometer survey data by Farsalinos and others (2016). Claims were made that vaping "caused 6.1m European smokers to quit smoking" (recently repeated in an article in the *Sydney Morning Herald* by Dr. Colin Mendelsohn - http://www.smh.com.au/comment/ecigarettes-needed-to-get-more-adults-to-quit-smoking-20170625-gwybcb.html)

This causal factoid has been widely promoted through social media, but was demolished in the journal *Addiction* where it was published [Maziak & Taleb, 2016]. Among other criticisms, the critics in *Addiction* asked:

> "how many of those who claim that they have stopped with the aid of e-cigarettes would have stopped anyway, and how many of those who used an e-cigarette but failed to stop would have stopped had they used another method?"

They also noted that the questions asked in the survey would have allowed those who quit for only a short period to say they had "stopped".

Longitudinal studies with a minimum of 12 months follow-up of randomly selected cohorts have shown sobering results, a long way from the hype of vaping having the equivalent

efficacy of antibiotics (Nutt D, 2013: https://www.youtube.com/watch?v=8rYSFiyZhwQ). One such study reported that:

> "Daily use of e-cigarettes while smoking appears to be associated with subsequent increases in rates of attempting to stop smoking and reducing smoking, *but not with smoking cessation.*" (our emphasis, Brose et al, 2015)

A companion paper [Hitchman et al, 2015] reported that daily tank system users were the only type of ENDS which showed a significant improvement in smoking cessation, although, the number of self-reporting vapers using these systems in that study was only 19.

Further, there are data which demonstrate that, for England, there are important differences between self-reported abstinence and biochemically verified abstinence. As West et al note:

> "Self-reported cigarette and total tobacco smoking prevalence were assessed by means of the standard questions used . . . In subsamples, specimens were collected for analysis of cotinine (saliva, N = 1,613 in England . . .) providing an objective means of determining active smoking . . . Self-reported cigarette smoking prevalence using the standard methods underestimated true tobacco smoking prevalence by an estimated 2.8% in England . . . Cotinine concentrations in those misclassified as nonsmokers were indicative of high levels of smoke intake. Interpretation: Underestimation of smoking prevalence was significant in England . . .". [West et al, 2007]

The same study identified no such discrepancy in U.S. data, and therefore, the validity of English ENDS survey data not utilising biochemical verification should arguably be viewed with this evidence in mind.

Not approved as cessation devices in USA

The current scientific evidence base does not, therefore, support recommending these devices as effective in smoking cessation. They are not approved as cessation aids by the US FDA [Brandon et al, 2015], nor by the US Preventive Services Task Force (USPSTF) which concluded "that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults, including pregnant women" [USPSTF, 2015], an analysis with which we fully agree.

What are the limitations of personal testimonies in establishing evidence?

"the plural of anecdote is not evidence".

Dr Tom Frieden, former Director of the US Centers for Disease Control and Prevention

The Committee will receive many testimonies from former smokers who will passionately explain that they were able to stop smoking by using ENDS. Many will argue that their experience self-evidently means that many others will, like them, also stop smoking after using an ENDS. Some of these will have been generated by tobacco companies such as Philip Morris, which have solicited such submissions to the inquiry. (see http://www.abc.net.au/radio/melbourne/programs/mornings/big-tobacco-spamming-punters-to-submit-to-government-inquiry/8667096)

Personal testimonies can also be found from ex-smokers on websites promoting smoking cessation strategies which are been shown under controlled research conditions to have very poor outcomes. These include acupuncture, "laser therapy" (see for example http://www.imaginelaserworks.com/additional-services/stop-quit-smoking/) and hypnosis, all of which have been assessed as being supported by very poor evidence of assisting smoking cessation. Those working in tobacco control are very familiar with a wide range of cessation approaches promoted by some quitters as the only or best approach because they worked for them. These range from astringents to herbal remedies to 5 Day Plans to clinics to books.

No one respectful of evidence gives any credibility to such personal testimony for cessation methods known from high quality reviews of evidence to be of poor efficacy. We should hold claims about the efficacy of ENDS in cessation to the same standards.

Those who quit smoking after using ENDS understandably attribute their smoking cessation to ENDS. Some want to spread their good news and encourage others to try to do what they have done. However, those who have tried and failed to quit using ENDS i.e. the substantial majority are far less likely to be as enthusiastic and evangelical. Positive personal testimonies represent flagrant self-selection bias about success and cannot be given any credibility when it comes to making generalisations about the success or otherwise of a cessation method.

What proportion of long-term users of vapourisers still smoke? ("dual use")

The significant majority of adult smokers who try ENDS to quit smoking stop using them [Simonavicius et al, 2017; UK Office for National Statistics, 2016]. Most adults who use ENDS continue to smoke conventional cigarettes ("dual users"). In 2014 in the US, 93% of ENDS users continued to smoke cigarettes [Patel et al, 2016], 83% in France [Andler et al, 2016], and 60% in the UK [UK Office for National Statistics, 2016].

It is essential to highlight here that even ardent advocates of ENDS point out that:

> ". . . concern(s) have been {partly} expressed that dual use" may encourage "smokers who could otherwise have quit elect for dual use instead, *in the mistaken belief that this generates significant health gains*" [our emphasis: Royal College of Physicians, 2016]

Professor Robert West (a leading figure in tobacco cessation research and director of the large *Smoking in England* national study told the BBC in February 2016, (http://www.bbc.co.uk/programmes/b070dq8h)

> "[This widespread use of e-cigarettes] raises an interesting question for us: If they were this game changer, if they were going to be – have this massive effect on everyone switching to e-cigarettes and stopping smoking *we might have expected to see a bigger effect than we have seen so far which has actually been relatively small*" [our emphasis]
>
> "We know that most people who use e-cigarettes are continuing to smoke and when you ask them they'll tell you that they're mostly doing that to try to cut down the amount they smoke. But we also know that if you look at how much they're smoking it's not really that much different from what they would have been doing if they weren't using an e-cigarette. *So I think as far as using an e-cigarette to reduce your harm while continuing to smoke is concerned there really isn't good evidence that it has any benefit*." [our emphasis]

As background to this statement, West et al (2016) estimated that between 16 000 and 22 000 extra smokers may have quit per year in England because of ENDS use, above and beyond the number who would have quit in the absence of ENDS. At a population level this equates to a change in smoking rates of 0.044-0.061%. This figure can be placed into perspective when looking at the average annual fall in smoking prevalence that Australia (which has insignificant ENDS use) in the 25 years between 1991 (29.5%) and 2016 (14.9%). Australia has achieved an average annual fall *10 fold greater* than the median estimate of 0.05% contribution calculated for ENDS by West et al. This ratio is similar if only the recent period 2010-2016 is examined. This small potential benefit would naturally have to be considered in conjunction with known ENDS harms.

	1991	1993	1995	1998	2001	2004	2007	2010	2103	2016
Daily	24.3	25	23.8	21.8	19.4	17.5	16.6	15.1	12,8	12.2
Weekly	2.8	2.3	1.6	1.8	1.8	1.6	1.3	1.5	1.4	1.3
< weekly	2.4	1.8	1.8	1.3	2	1.6	1.5	1.4	1.6	1.4
Total	29.5	29.1	27.2	25.9	22.2	20.7	19.7	18	15.8	14.9

Smoking in Australia, persons aged 14+ 1991-2016
Source: Australian Institute of Health and Welfare

West et al (2016) described their estimations thus:

> "Evidence from RCTs and from surveys in England indicate that using an e-cigarette in a quit attempt increases the probability of success on average by approximately 50% compared with using no aid or LNP bought from a shop—similar to use of a licensed medicine with limited behavioural support but less than medication plus specialist behavioural support [6,7].".

The two references the authors used here were the Cochrane Collaboration review [Cochrane, 2016] (which noted that the evidence for smoking cessation with ENDS was low to very low) and a cross-sectional study [Brown et al, 2014] which have the weaknesses we described above. With the caveats that must apply to these sources, we would submit that no firm conclusions as to effect size can be credible, considering the fragility of these data.

The Committee should therefore be most circumspect in considering claims that ENDS use in the UK has caused a dramatic fall in smoking rates.

Very recent data from England show that about half of daily ENDS users are also smoking (Figure 1 below) and that the rate at which English smokers have tried to stop was the lowest in 2016 (30.9%) than it had been since 2007 (42.5%) when the study began (Figure 2 below). The decline in those attempting to quit is 11.6% in absolute terms and 27.3% in proportional terms. These are very disturbing data which would greatly please those in the tobacco industry.

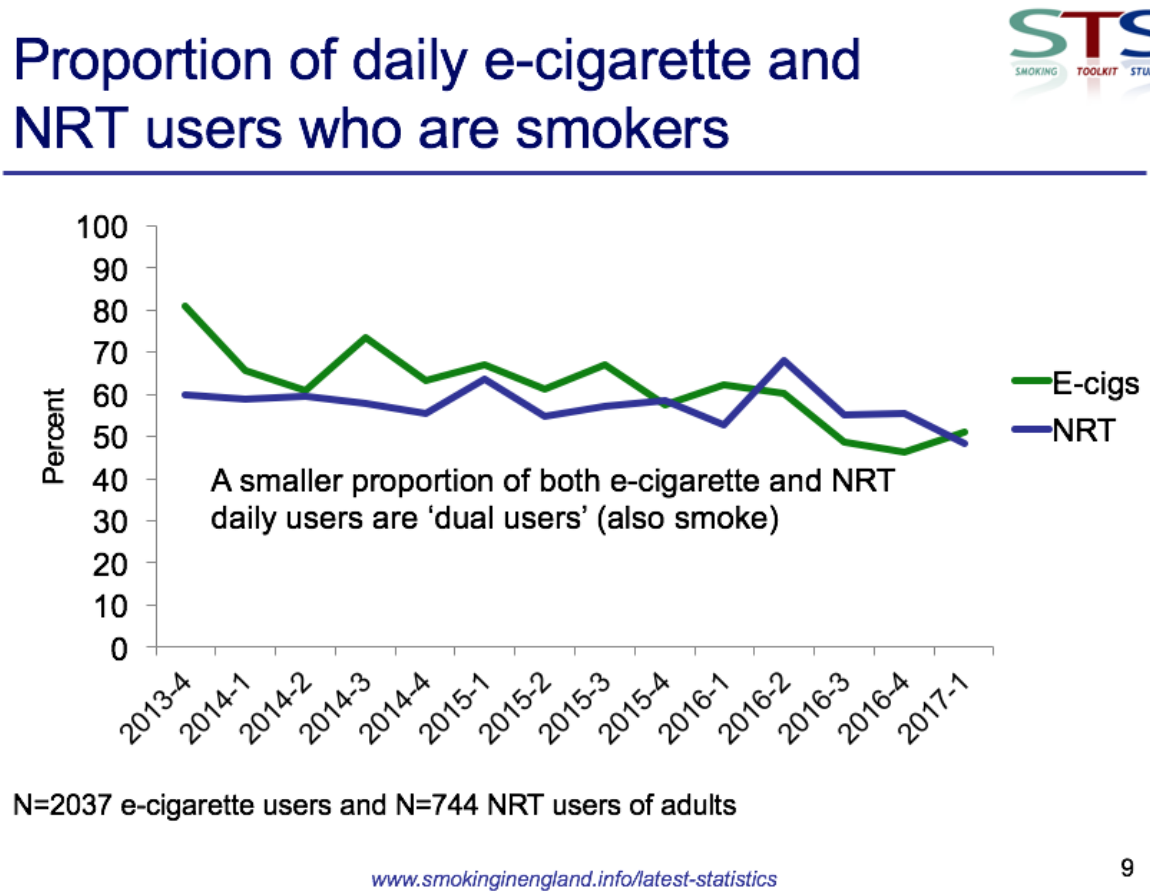

Figure 1: About half of daily e-cigarette users in England are currently also smoking cigarettes

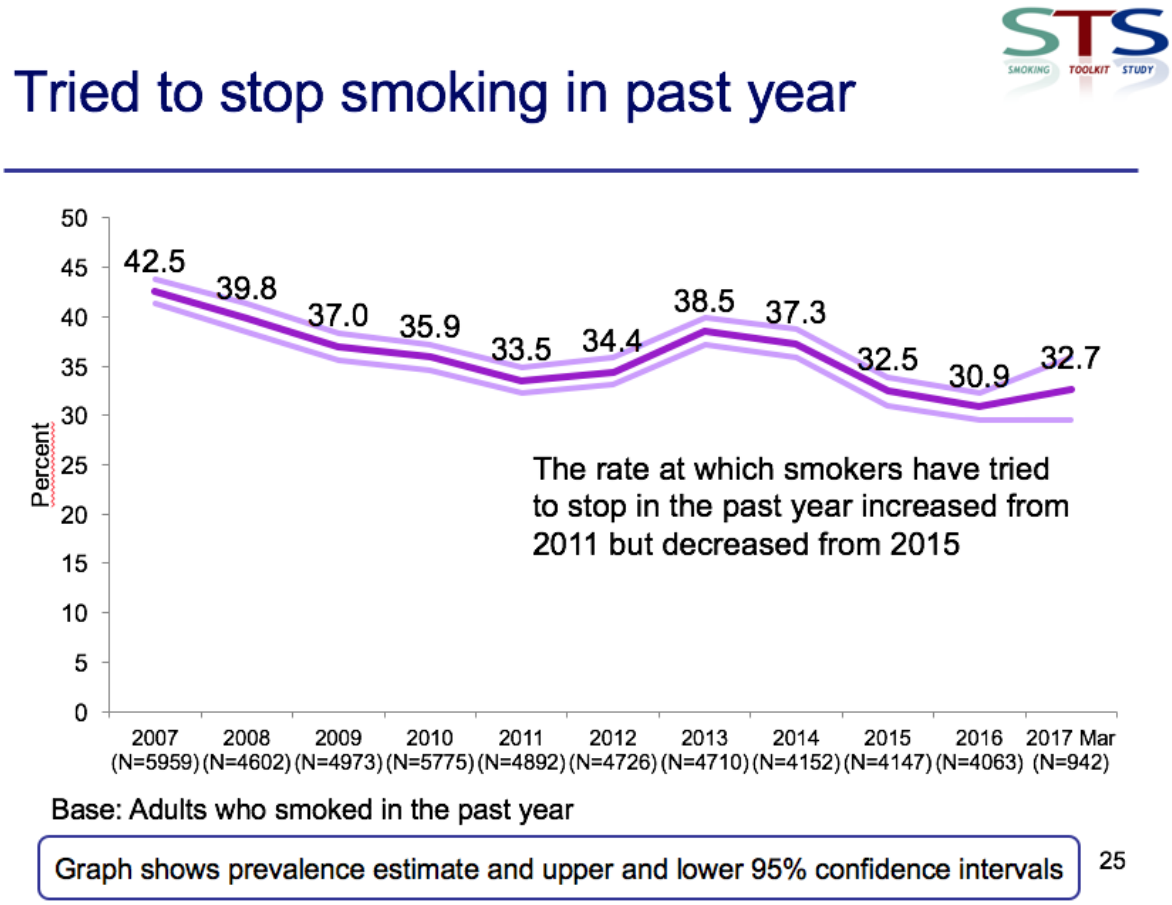

Figure 2: Continuing decline across 10 years in percentage of English smokers trying to stop smoking (e-cigarettes became available from around 2007)

These data raise important questions about whether ENDS may be holding many smokers in smoking even if they help some to quit. Moreover, new data concerningly suggest that non-daily vapers may actually *increase their consumption* of conventional cigarettes [Doran et al, 2017]. Further, it has been suggested that one of the key reasons for US cigarette consumption being higher higher in 2015 than in 2014 (the first time cigarette consumption increased since 1973) [Wang T et al. 2017], was because of continued dual use. Recent qualitative data, where dual users are asked about their continued smoking and vaping behaviours, suggests that dual users may find it harder to quit, as they do not actually view themselves as smokers [Vandrevala et al, 2017].

Key questions for public health therefore include: what is the net impact of the widespread use of ENDS? Does the proliferation in ENDS use tip more people permanently out of smoking than it holds in smoking? Does it pull significant numbers of ex-smokers back into nicotine dependency? Does it see children who may have never used any form of nicotine

product start vaping or encouraged to think of vaping or smoking as normal and acceptable behaviour for them? What might be the health effects of long term vaping?

Marketing

Interest groups promoting ENDS understandably wish to be allowed to promote their products to as wide an audience as possible. These groups are generally cognisant of the need to at least appear to be acting responsibly, by claiming they do not want children to use ENDS. However, the reality with ENDS at the retail level suggests the opposite. Results of a recent UK Chartered Trading Standards Institute investigation [CTSI, August 2016] identified that approximately 40% (246/634) of retailers illegally sold nicotine e-cigarettes and vaping liquids to children and young people, with 50% (68/137) specialist vaping shops "flouting" laws regarding the selling ENDS and nicotine e-liquids to children.

Another example of this was exposed recently by the UK Royal Society for Public Health [RSPH, 2017], which undertook an undercover investigation of 100 of the UK's 1700 independent vape shops. Nearly nine in 10 stores (87%) were either knowingly, or unwittingly, selling ENDS to people who have never smoked or vaped. As was highlighted by the RSPH:

> "Almost half (45%) of stores did not check whether new customers were current or former smokers."
>
> "Three quarters (76%) of those that did check continued to encourage the customer to start vaping, even once they knew they were a non-smoker."
>
> "This is in direct violation of the Independent British Vape Trade Association (IBVTA) code of conduct which states: "Vape products are for current or former smokers and existing users of vaping devices, therefore never knowingly sell to anyone who is not a current of former smoker, or a current vaper." (http://www.ibvta.org.uk/join-us/code-of-conduct)

"The code of conduct exists to ensure e-cigarettes are perceived as an effective aid for quitting smoking, rather than as a lifestyle product" [RSPH, 2017].

Allegations of "irresponsible" marketing tactics utilised by elements of the ENDS industry were recently made by Dr K Farsalinos, a vociferous advocate for the potential of ENDS to help adult smokers quit, who stated:

> "I wonder if there is anyone who thinks that the use of cartoons and funny graphics . . . is not going to be perceived as appealing, and an attempt to actively promote the products, to youth . . . this is absolutely unacceptable and a clear indication of irresponsible behaviour . . ." (Farsalinos, 2017)

Industry claims of being public health allies are obviously nothing but cynical public relations gestures because, like all industries, the future of ENDS commerce depends on new users. With ENDS, this means non-users of ENDS taking them up and becoming addicted to nicotine via ENDS. Smokers are an obvious target, but children are another which cannot be airbrushed out of public policy considerations (see Term of Reference #5 below).

The same tobacco companies which are now heavily investing in ENDS have always strenuously publicly denied that they do not want children to smoke.

Voluminous evidence from their own internal documents reveals that such statements were duplicitous public relations statements [Assunta & Chapman, 2004; Knight & Chapman, 2004]. If the ENDS industry is to survive, and flourish, it will need to attract new users: adult smokers, adult non-smokers and youth, which it appears to be attempting to do. It is manifestly in the interests of tobacco companies and any others involved in the e-cigarette industry that children and young people should view their products favourably and be encouraged to use them. Any denials on this issue carry as much credibility as tobacco industry denials over the decades.

The figure below shows an example of the sort of packaging and promotional appeals that have been seen in England recently. This link shows examples of ENDS promotions with major appeal to children in the USA
http://www.tobaccofreekids.org/tobacco_unfiltered/post/2015_06_17_ecig

Figure: child-attracting vaping products on sale in England, 2016

As the University of Bath Research team point out "E-cigarettes are being marketed in a way which emulates very successful tobacco advertising asserting an independent identity and a lifestyle choice, aligning oneself with celebrities, fashionable and youthful places and activities."

The current bill before the Senate presented by Senators Leyonhjelm and Roberts (Vaporised Nicotine Products Bill 2017) seeks to allow the advertising of ENDS through

changes to the Tobacco Advertising Prohibition Act 1992. There is no known form of advertising which can only be seen by adults but not by children. Should this Bill succeed, ENDS marketers would be effectively free to promote their products, brand names and corporate identities to the entire community, including (non-smokers as well as smokers, children and young people. We would doubtless witness the same farcical and totally ineffectual "safeguards" against this as we witnessed with assurances about non-appealing advertising and children with tobacco advertising in the 1980s and even earlier. It is indeed fifty years since the late Senator Robert Kennedy said in 1967,

> "If we were starting afresh, I would say the first line of action would be industry self-regulation of advertising. But we have witnessed a charade of purportedly self-regulation for some years. The codes of self-regulation have been largely ineffective, and I see little hope for change. The industry we seek to regulate is powerful and resourceful. Each new effort to regulate will bring new ways to evade".

Giving the tobacco industry or any others carte blanche to advertise e-cigarettes would be a catastrophic error - yet another demonstration of the need to respect the processes of the TGA.

Below are photographs taken in NSW of ENDS products being sold alongside confectionery at eye-level, where young children would easily see them. Tobacco products are required to be stored out-of-sight in all Australian states and territories. We believe the same regulations should apply to ENDS products.


Skittles
Skittles
Skittles
Wobl Bobba
Wobl Bobba

Term of Reference #2. The health impacts of the use of e-cigarettes and personal vaporisers

Unlike inhaling tobacco smoke from combusted tobacco products, inhaling vapour does not involve inhaling the smoke arising from combusted tobacco. That smoke contains carbon monoxide, tar, many carcinogens and co-carcinogens, toxicants and irritants. ENDS do not ignite the contents of the liquids which are vapourised. They instead heat them, and so there is no carbon monoxide or "tar".

From this, it has been argued that inhaling vapour will be eventually acknowledged to be of *far* less risk to health than smoking. However, many ENDS advocates are adamant that we know this to be true already, barely a decade after ENDS use began to be used widely in some countries.

They argue that there is no need to wait any longer before adopting policy based on assumptions that ENDS are all but benign, and accordingly ENDS should be treated as such.

They argue that smoking now kills 7 million people a year and will kill an estimated 1 billion during this century and that widespread use of ENDS will see such figures dramatically reduced. This would be self-evidently a wonderful thing if it their predictions were to be later shown to be correct. But as we will argue, the evidence that we have confidence that we currently have to inform these predictions is very scant. There is also overwhelming evidence that tobacco companies selling and promoting ENDS are indeed doing all they can to continue to aggressively promote cigarettes - and hence the deaths they cause - in both developing and developed countries.

Tobacco control has had a long history of wild, unbridled and commercially driven enthusiasms for purported reduced harm products (filters, asbestos filters, reduced carcinogen cigarettes, "low" tar, "lights", tobacco substitutes, etc). None of these were subsequently demonstrated to reduce harm is those who used them. [Parascandola, 2011}. It does not follow from this that ENDS will similarly be found to fail as harm reduction devices, but the long history of failure and the consequences of again promoting false hopes must give all responsible authorities strong pause for consideration.

This submission is not a formal, systematic review of the research literature on ENDS. However, our concern is to give some perspective to the obvious campaign by ENDS

advocates to present an entirely sanitized view of what is known about the health risks of ENDS use.

There is a rapidly growing toxicological research literature on the health effects of ENDS.

Appendix 1 below shows an indicative recent selection of such research. No one reading this research who had an open mind as to whether ENDS might be seriously harmful could form the view that they were free from serious concerns and should be sold as freely as grocery items, let alone widely promoted.

With respect, parliamentary committees are not in a position to assess the scientific quality of specialised toxicological research such as that we have highlighted in this submission and in Appendices 1 and 2 . In Australia, that is very obviously and properly the role of expert bodies like the TGA and the NHMRC which can convene and commission independent scientific expertise to advise governments.

Both have already done this with ENDS.

Is it too soon to know whether vapourisers are really far less dangerous than cigarettes?

It has been claimed, utterly bizarrely, by some that:

> "The paucity of evidence for serious harm to users of e-cigarettes over the years since they were first marketed in 2006, with millions purchased, in itself is evidence" that they do not cause such serious harm (Nutt et al, 2016).

The main diseases caused by smoking (cancers, respiratory and cardiovascular) are known as chronic diseases. While there can be some people who manifest smoking-caused health problems early, clinical signs of diseases like lung and heart diseases and cancers typically begin to show up in larger numbers several decades later. The harms of smoking do not manifest quickly in the ways that those resulting from exposure to infectious or acutely toxic agents do. The aforementioned claim by Nutt et al is, therefore, at odds with what is well established with conventional cigarettes.

Smoking skyrocketed when cheap, affordable cigarettes first appeared early in the twentieth century following the invention of mechanised cigarette rolling machines. Over the next 20 years, lung cancer remained an uncommon, even rare disease.

The US surgeon Alton Oschner, recalling attendance at his first lung cancer autopsy in 1919, was told he "might never see another such case as long as we lived". He saw no further cases until 1936 -- 17 years later - and then saw another nine cases in six months. Today lung cancer is (by far) the world's leading cause of cancer death.

The incidence of lung cancer rose rapidly in the decades 1930-1980 but it was not until 1950 that definitive evidence was published in the USA and the UK that long-term smoking caused lung cancer, by far the most common form of fatal cancer today. Knowledge about smoking's causal role in other diseases followed.

If any scientist had declared in 1920 that cigarette smoking was all but harmless, history would have judged their call as dangerously incorrect. But this is the reckless call that many ENDS advocates are making today, after just 10 years.

What is the provenance of the claim the e-cigarettes are "95% safer" than cigarettes?

This number was produced by a hand-picked group of 12 [Nutt D et al, 2014] who were asked to rank the health risks of 12 nicotine delivery products, including cigarettes. Several of the group had no research track record or expertise in tobacco control and some had histories of financial connections with manufacturers of ENDS and tobacco companies [Gornall, 2015]: a network diagram from the British Medical Journal (http://www.bmj.com/content/351/bmj.h5826/infographic) shows these interconnetions between some of the authors. The authors stated that "There was no formal criterion for the recruitment of the experts although care was taken to have raters from many different disciplines."

However, there were no toxicologists, cancer or cardiovascular specialists among the authors. The "95%" number was uncritically repeated in a Public Health England (2015) review and report, which amazingly even described e-cigarettes as "around 95% *safer* [not *less dangerous*] than smoking" (our emphasis). Incredulous toxicologists have since pointed out: "there is no *evidence* for the 95% estimate" [their emphasis, Combes & Balls, 2015]

Even the pro-ENDS activist Carl Phillips, who has a long history of support from tobacco manufacturers (see http://www.tobaccotactics.org/index.php/Carl_V_Phillips), summed up this study as follows:

> "This specific point estimate (synonymous with "5% as bad for you as smoking") has rapidly evolved into "fact" (in the political sense of that term). It is repeated in a large fraction of popular press reports and widely used in arguments, snipes, and broadsides from vaping advocates. *It seems to have emerged from nowhere* when the

> Public Health England report asserted the figure. That traced to what was *actually a huge misinterpretation of what was only a made-up number, from one junk-science journal article*." (our emphasis) https://antithrlies.com/2016/05/25/saying-e-cigarettes-are-95-less-harmful-is-a-very-bad-idea-part-143-of-10000/

Moreover, several UK organisations which have cited this paper as being central to their perspectives (e.g. Public Health England; Royal College of Physicians; NHS UK) appear not to have noticed that the group of twelve authors themselves stated that:

> "A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria."

So, a group of 12 people estimated that ENDS were 95% less dangerous than cigarettes, despite acknowledging themselves that they had a "lack of hard evidence of most products on most of the criteria" for their guess. This is hardly surprising, as this risk estimation exercise was carried out in the summer of 2013, just a few years after ENDS devices became readily available to consumers.

Bizarrely, the authors of the "study" subsequently attempted to respond [Nutt et al, 2016] to extensive criticism of it [Lancet, 2015] by attempting to counter the correct observation that their study suffered from, among other things, a lack of hard evidence. As noted above, they had, *themselves*, explicitly stated in the original article that this *was*, indeed, the case.

Didn't both the Public Health England and the Royal College of Physicians reports on e-cigarettes endorse the "95% safer" figure?

Yes they did, however, neither of these two groups provided any data, calculations or formal risk assessment to substantiate the production of the "95%" figure, nor indeed, any possible figure. They would have appeared to have just repeated the same, identical opinion-led "justifications" originally published by the Nutt et al group.

So what is the true risk of e-cigarettes compared with cigarettes?

We have often been asked "well, if you question the risk as being 95% less dangerous, what is *your* estimate?" Those asking this question appear to not understand that no estimate can be made currently that has any acceptable toxicological degree of accuracy. This is the opinion of expert toxicologists, who have noted:

> " . . . Public Health England and the Royal College of Physicians in the UK, largely relied on expert opinion and where evidence was considered it largely focused on studies of vaping aerosol and e-liquid composition with relatively few biomarker studies . . ."[Wilson et al, 2016]

Their subsequent analysis of the few recent relevant biomarker studies available at the time of their review revealed a:

> ". . . very diverse range of results . . . but all suggest lower levels of risk for vapers compared to tobacco smokers". However, "preliminary evidence . . . suggests that the effect of vaping on four . . . inflammatory markers of likely relevance to cardiovascular disease (CVD) and respiratory disease may be at least half that of tobacco smoking" and "The results for cancer-related toxicants were variable, from 0% to 23% of the levels observed for tobacco smokers, with most studies reporting between 14% and 23% – *a substantial level of exposure***"** [Wilson et al, 2016, our emphasis].

Because of the relatively few years in which people have vaped, it is not currently scientifically possible to provide a credible single figure estimate of risk. The World Health Organisation confirmed this when they stated:

> "The magnitude of these risks is likely to be smaller than from tobacco smoke although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products. Therefore, no specific figure about how much "safer" the use of these products is compared to smoking can be given any scientific credibility at this time" [WHO, 2016]

Two toxicologists put it rather more bluntly, that to label ENDS as "low risk" products is:

> "*in the light of current knowledge*, a reckless and irresponsible suggestion" . . . such a view "ignores the possibilities that users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation." (their emphasis, Combes and Balls, 2015).

As key co-authors of the 2016 UK RCP "Nicotine without smoke" review stated at the same time that the RCP review was published, ENDS are highly unlikely to be harmless:

> "long term use is likely to be associated with long term sequelae, including an increased risk of chronic obstructive pulmonary disease, lung cancer, possibly cardiovascular disease, and some other long term conditions associated with smoking" [Britton et al, 2016; WHO, 2016] i.e. sequelae associated with the well-documented spectrum of harm caused by smoking conventional cigarettes .

Vaping advocates urge smokers to switch to ENDS. Those who fully switch are likely to experience reduced risk of premature death from smoking caused diseases, but the magnitude of that risk remains entirely speculative, in the absence of any large longitudinal population studies.

How often do vapers inhale vapour?

In 2014, the US tobacco company Lorillard posted on a website advising parents about how they could talk to their children about vaping, claiming, misleadingly and irresponsibly, that:

> *"The 'smoke' you see coming out of e-cigarettes isn't smoke -- it's WATER VAPOR.*"

(http://www.tobacco.ucsf.edu/sites/tobacco.ucsf.edu/files/u9/What%20you%20need%20to%20know%20about%20e-cigarettes%20%E2%80%93%20Infographic%20_%20Real%20Parents%20Real%20Answers_may31-2014.pdf *and*

http://www.tobacco.ucsf.edu/lorillard-maker-blu-ecigs-tells-parents-ecigs-just-emit-harmless-water-vapor-thats-not-true)

Vapers average about 200 inhalations a day, with a 2016 study [Martin et al, 2016] finding a range of 6 to 611 puffs, an average 73,050 deep lung bastings a year, up to 223,168. Like cigarette smoke, vape mist normally contains, as well as nicotine, normally, a cocktail of toxic contaminants and by-products, for example, proinflammatory fine, ultra-fine and nano-particles [Fouco et al, 2013], potentially harmful and carcinogenic metals and silicate [Williams et al, 2013; Hess et al, 2017], toxic and carcinogenic aldehydes [Kosmider et al, 2014], and potentially cytotoxic flavourings [Farsalinos et al, 2015]. It is *anything but* just like "inhaling steam in a shower", as some on vaping blogs have irresponsibly tried to describe it.

Lung Health

The primary target or site of inhaled ENDS vapour is the lung. The lungs have a combined surface area the size of a tennis court and are hugely exposed to vapourised products. For organic compounds, other chemicals and heavy metals, in vapour that can be absorbed into the lung circulation, there is a broad access avenue. Normally, the lungs have a critical surface fluid lining that is vanishingly thin so that the volume of this fluid is less than 5mls. At the conclusion of a vaping session, it has been estimated that half of the lining fluid composition is derived from the vaping inhaler. [Manigrasso, M., et al 2015]

This is critically different from an asthma spray. 99% of the propellant of an asthma spray is exhaled unaltered in gaseous form with the active drug in powder form being left behind (Leach, 2005).

Further, for the majority of ENDS users who are also current smokers, the altered lung lining fluid may actually increase exposures to toxins within cigarette smoke. Normal lining fluid is little more than salty water and fat-based toxins from smoke cannot dissolve in it. [Fröhlich, 2017]. In contrast, by its very nature, ENDS vapour is an excellent solvent. Changing the properties and constituents of lung lining fluid may, for example, change the absorption and effect of common treatments for asthma or alter in a very deleterious fashion cigarette smoke particle transit in the majority of ENDS users who continue to smoke .

That this change in the lung liquid interface is a real, and not just a theoretical, risk is supported by data from aviation safety training that shows changes in the basic properties of tear fluid in the eyes from propylene glycol [included in almost all ENDS] exposure in aviation safety training exercise.

A highly detailed review of the lung toxicity of ENDS has recently been published in the *American Journal of Physiology* [Chun et al, 2017]. This was funded by the US FDA and the National Cancer Institute. The review concludes:

> "In summary, there is a rapidly growing body of evidence derived from in vitro, animal, and human studies that e-cigarette use may have *significant pulmonary toxicity.*" (our emphasis)

Specific harms that the review addresses include:

A. Harms in adolescent ENDS users

In a study of 45,000 adolescents in Hong Kong, use of ENDS in the preceding 30 days doubled the risk of cough and phlegm in both ever smokers and never smokers [Wang et al 2016]. In a separate study of 40,000 adolescents in South Korea, ENDS use more than doubled the risk of asthma being diagnosed and more than trebled the frequency of school absence related to asthma.[Cho & Paik 2016] These harms are real, immediate and a cause for concern about protecting children from ENDS whether containing nicotine or otherwise.

B. Harms of flavourants and other vehicle compounds.

ENDS contain many flavourants that are approved for oral ingestion but not for inhalation. Further, the superheated environment in ENDS alters these chemicals to definite toxins and higher levels of toxins, equal to or greater than those seen in cigarette smoking. This can be seen when variable power devices are set to their highest setting. In particular the carcinogen formaldehyde and other aldehydes may be present in higher concentrations (Khlystov and Samburova, 2016).

C. Harms of heavy metal exposures

The heating coil for ENDS can easily decay or flake and cause toxic heavy metals to be included in solution or as a particle in the vaped aerosol. These include nickel, chromium and aluminium. All are carcinogens and all are better not inhaled. Silicates that are also carcinogenic may also be formed. [Williams et al 2013]

What do we know about the health consequences of inhaling nicotine many thousands of times a year?

ENDS advocates have sought to trivialise the health risks of nicotine, regularly sheltering behind the slogan:“People smoke for the nicotine but die from the tar” [Russell, M. 1991]

The inhalation of nicotine, however, may be anything but benign. The International Agency for Research on Cancer [IARC, 2014] recently noted that they had not previously evaluated electronic cigarettes and nicotine. They describe current evidence, and note that “recent evidence has indicated the potential for nicotine to cause DNA damage” and “In addition, exposure to nicotine has been shown to inhibit apoptosis, and stimulate cell proliferation and angiogenesis . . .”. Subsequently, due to their rapid uptake as consumer products in

many countries, the IARC declared that an evaluation of electronic cigarettes and nicotine is a "High Priority".

Appendix 2 lists recent research reports about the possible role of nicotine as a cancer promoter. This growing area of research underscores why it remains entirely appropriate that nicotine should remain within the regulatory oversight of the TGA in Australia.

There is no ENDS device that is a purely nicotine delivery system. Most ENDS deliver nicotine, which has its own toxicity as well as, clearly, the well documented effect of psychophysiological addiction. But they also deliver a variety of chemical vehicles/solvents, flavours etc that are separately and perhaps cumulatively toxic, and none of which are approved for inhalation in the form that they are included in solutions or in any chemically altered form that might emerge after superheating. As has been articulated by toxicologists:

> ". . . users might be repeatedly exposed to hitherto undetected contaminants and by-products, as well as to carcinogenic chemicals, or their precursors (which have been detected in solvent extracts and vapours, and which are derived from tobacco during solvent extraction or generated during solvent heating), that can have effects at very low dose levels, following repeat exposures, which can occur without clear threshold doses, thus necessitating zero-dose extrapolation" (Combes and Balls, 2015)

Many vapers reduce how much they smoke. Isn't reducing smoking obviously harm reducing?

Recent studies with small groups of subjects [Goniewicz et al, 2017; Shahab et al, 2017] indicate that smokers who fully switch from from cigarettes to ENDS reduce their exposure to various carcinogens and toxicants. They highlight, however, that "e-cigarettes are likely to be beneficial only if complete cessation of combustible cigarette smoking is achieved" [Shabab et al, 2017]. As we have discussed, large proportions of ENDS users are dual users and continue to smoke, so are highly unlikely to be reducing harm.

While there is strong evidence for a causal association between early uptake, amount smoked and duration (pack years) of smoking, the evidence on "reverse engineering" harm by continuing to smoke while cutting back is far from strong.

A Norwegian cohort of 51,210 people followed from the 1970s until 2003 found "no evidence that smokers who cut down their daily cigarette consumption by >50% reduce their risk of premature death significantly" [Tverdal & Bjartveit K. 2006]. A Scottish study [Hart et al, 2013] of two smaller cohorts followed from the 1970s to 2010 found no

evidence of reduced mortality in reducers, but clear evidence in quitters and concluded "that reducing cigarette consumption should not be promoted as a means of reducing mortality." The largest study, from Korea [Sung et al, 2008] and involving 479,156 men followed for 11 years , found no association between smoking reduction and all cancer risk but a significant decrease in risk of lung cancer, with the size of risk reduction "disproportionately smaller than expected".

A 2007 systematic review of the evidence on the health impact of reduction which included none of the above important studies, noted that most studies examined reductions in smoking of more than 50%. It found:

> "A substantial reduction in smoking seems to have a small health benefit, but more studies are needed to determine the long-term effects of smoking reduction" [Pisinger and Godtfredsen, 2007].

The apparently commonsense argument that it must be self-evidently true that continuing to smoke, but only smoking less than before, is harm reducing is therefore very poorly supported by research evidence.

What do we know about inflammation associated with vaping?

We have emphasised that it is far too soon to know at the population level whether widespread vaping will cause significant health problems, or health gains. We have further noted that vapers who stop smoking and fully switch to ENDS are exposed to much lower levels of many toxic and carcinogenic substances [Goniewicz et al, 2017; Shahab et al, 2017].

However, serious health effects can be observed when exposure to doses of such substances are very low [Combes & Balls, 2015]. For example, there is evidence that the dose-response curve for the potent lung carcinogen NNK, as identified in e-cigarette aerosol [Goniewicz et al, 2013] is highly nonlinear, has no clear threshold, with substantial increases in occurrence of lung cancer at very low doses [Hengstler et al, 2003, Figure 9, cited in Combes & Balls, 2015].

Recent independent comprehensive reviews of the current literature on health risks are available, and highlight both potential cardiovascular risks [Bhatnagar et al, 2016; Schweitzer et al, 2017)] and respiratory risks [Chun et al, 2017]. For example, Glycerol, one of the two solvent agents utilised in delivering nicotine and flavourants in e-cigarette fluid, when heated to even very low temperatures (relative to combustion temperatures), has been known for at least 90 years to thermally decompose and form, among other

chemicals, the highly toxic aldehyde acrolein [Lawrie, 1928]. The smell of burnt fat, when cooking oil is heated, is caused by glycerol in the burning fat breaking down into acrolein; there is growing evidence that chronic inhalation of such cooking fumes is related to lung disease [Juntarawijit C & Juntarawijit Y, 2017] . As the aforementioned reviews show, low dose acrolein has the potential to cause both respiratory and cardiovascular disease [Chun et al, 2017; Bhatnagar et al, 2016; Schweitzer et al, 2017]. Inhaled low dose acrolein has been strongly associated with causing chronic pulmonary inflammation i.e. COPD, a reduction of host respiratory defenses, neutrophil inflammation, mucus hypersecretion and protease mediated lung tissue damage [Moretto et al, 2012]. Moreover, "prolonged exposure to even low-dose . . . acrolein results in nonspecific inflammatory cardiac lesions" [Bhatnagar et al, 2016].

On the crucial issue of aldehyde exposure, a highly critical review of a key paper postulating that users of ENDS do not inhale significant levels of acrolein and other toxic aldehydes (e.g. formaldehyde, acetaldehyde) [Shihadeh et al, 2015] highlighted substantial problems with the paper. Shihadeh et al (scientists active in the field of electronic cigarettes, including exposures to aldehydes), highlighted that the criteria commonly considered during peer review (i.e. that "the method be described sufficiently so as to allow replication, results and data analytical techniques are presented thoroughly, and conclusions are based on the results presented") were "not met" by Farsalinos et al in 2015. [Farsalinos et al *Addiction*, 2015]

However, the Farsalinos et al (2015) study was uncritically cited by Public Health England 2015 as evidence that that puffs of ENDS aerosol, relatively rich in toxic aldehydes, are "instantly detected [by vapers] due to a distinctive harsh and acrid taste. This poses no danger to either experienced or novice vapers, because [such] dry puffs are aversive and are avoided rather than inhaled."

This presumption was based on only this one study of just seven vapers using unflavoured liquid. This flavouring issue is important, as some flavours are already known to potentially mask the harsh, acrid tastes of cigarettes, and therefore, potentially, ENDS [Alpert et al, 2015]. The original Farsalinos et al study itself recommended further studies to better understand interindividual differences in tasting perception. Longitudinal studies would further be needed in order to establish potential changes in perception: it has been correctly noted that some smokers, over time, learn to "overcome" and inhale puffs of cigarette smoke, rich in aldehydes [Rowell and Tarran, 2015]. These issues highlight the importance of: sticking to the scientific method; appropriate peer review; and of replication and expansion of results, *prior* to influential public health organisations making, in effect, unsubstantiated generalisations from one small study.

Highly reactive free radical production, also implicated in the causation of the irreversible inflammatory lung disease COPD from cigarette smoking, has also been identified in ENDS aerosol [Goel, 2015]. The volumes of highly reactive free radicals collected were, perhaps predictably, much less than those in found in cigarette smoke, presumably related to the absence of combustion in ENDS aerosol production. However, as the authors point out:

> "Since the overall levels of radicals are significantly lower than those observed in conventional cigarette smoke, it might be expected that the degree of damage might be less, but this depends on the identity and reactivity of the specific radicals produced" [Goel et al, 2015]

Research already carried out in human subjects (Martin et al, 2016) indicates that ENDS suppress genes involved in the immunity and inflammatory responses of users: the authors signal the necessity for further research into the respiratory consequences of vaping.

A very recent review of the potential cardiovascular risks of vaping concluded that:

> "The majority of studies found some evidence of a significant risk effect for e-cigarettes, although the evidence was not totally consistent within and between studies. Suggestive evidence also implicates a possible effect of e-cigarettes on inflammation processes. Levels of risk indicators for e-cigarettes were sometimes lower than those found for cigarettes but several studies showed comparable effects" [Schweitzer et al, 2017].

As noted above, ENDS work by creating an aerosol of ultrafine particles that carry nicotine deep into the lungs of users, and thereby into the bloodstream to the heart, and then to the brain. These particles are as small as – and sometimes smaller – than those in conventional cigarettes [Fuoco et al, 2014]. Importantly, these ultrafine particles are biologically active, and can trigger inflammatory processes that are directly implicated in causing cardiovascular disease, and acute cardiovascular events [Pope C et al, 2009]. The dose-response effect for exposure to these particles, similar to the above example of the potent lung carcinogen NNK, is nonlinear, with substantial increases in cardiovascular risk with even low levels of exposure to ultrafine particles [Pope et al, 2009]. There is some evidence, already emerging, of a potential link between ENDS use and increased risk of heart attacks [Temesgen et al, 2017. See link to full discussion of this new data in the Reference List].

ENDS expose users who fully switch to them to reduced levels of carcinogens, which may likely reduce their risk of cancer. However, it should be noted here that most of the premature, preventable deaths associated with smoking tobacco are related to cardiovascular and non-cancer respiratory disease, and not cancer [U.S. Department of

Health and Human Services, 2014], and that current interpretation implicates significant cardiovascular and non-cancer respiratory health risks .

Is it safe to inhale vapourised propylene glycol?

Propylene glycol (PG), like glycerol, is a chemical used in vaping liquid in which the nicotine and flavour chemicals are vapourised and transported into the lungs. There are some very old data on the effects of inhaled PG in animals [Robertson & Loosli, 1947], which are regularly cited in the literature relating to potential positive effects [e.g. Farsalinos and Polosa, 2014]. However, Dow Chemical, which manufactures PG, says unambiguously, reflecting data from *human* subjects (Weislander et al, 2001), that:

> ". . . breathing spray mists of these materials should be avoided. In general, Dow does not support or recommend the use of Dow's glycols in applications where breathing or human eye contact with the spray mists of these materials is likely…"
> (DOW, 2003)

Weislander et al highlighted that:

> "Short exposure to PG mist from artificial smoke generators may cause acute ocular and upper airway irritation in non-asthmatic subjects. A few may also react with cough and slight airway obstruction."

It has been incorrectly claimed by some that PG is a solvent utilised in the delivery of inhaled nebulised medications for asthma sufferers, and that, therefore, "it must be safe". **No standard asthma inhaler in Australia contains propylene glycol.** However, there is evidence that it is in fact the case that PG is used in this therapeutic fashion, although, it is "a commonly used drug solubilizer in topical, oral, and **a very limited number of i**njectable medications" (https://www.drugs.com/inactive/propylene-glycol-270.html).

This view has been articulated even by active advocates of vaping (Johnson L, 2016) who stated, subsequent to his own research, that he was completely unable to identify confirmatory evidence for PG being used in nebuliser therapy. He stated that the claim is fundamentally "misleading", and that, "as many vapers will know – some people find PG very irritating to the throat". Johnson continued to speculate on the genesis of the claim:

> "As for why this argument has gained so much traction, my only guess is for the same reason I want it to be true: it's so powerful to be able to say, "well, even asthmatics can inhale PG without problems, so worrying about it in e-cig vapor is

> silly." But when you really want something to be true, you don't have much motivation to go and check out whether or not it's really the case" [Johnson L, 2016]

Is it safe to inhale vapourised flavouring chemicals?

There are now some 8000 beguiling and often child-friendly flavours being sold in e-juice [Allen et al, 2016; Barrington-Trimis et al, 2014]. These have mostly been approved for ingestion as food additives, but have never been approved for inhalation. The U.S. flavouring industry has said about this issue:

> "The manufacturers and marketers of ENDS, and all other flavored tobacco products, and flavor manufacturers and marketers, should not represent or suggest that the flavor ingredients used in these products are safe because they have FEMA GRAS™ status for use in food because such statements are false and misleading." [see https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-electronic-nicotine-delivery-systems]

For some flavourants, for example cinnamon, there is already evidence for cytotoxicity [Behar et al, 2014] and for the very commonly utilised additive diacetyl, which produces a pleasant, buttery taste in e-liquid, there is an association with the causation of the non-reversible respiratory condition Bronchiolitis Obliterans [Farsalinos et al, 2015; Allen et al, 2016]. The English National Centre for Smoking Cessation and Training has already recommended that users avoid cinnamon and diacetyl flavoured e-liquid [NCSCT, 2016]but these are still on sale. Cherry flavoured ENDS fluids have also been demonstrated, via the inhalation of the irritant benzaldehyde, to be a potential concern for long term users [Kosmider et al, 2016].

Our knowledge of the impact of long term inhalation, many times a day over many years, of vapour arising from the heating of these chemicals is in its infancy. We therefore recommend adopting the precautionary principle to issues related to the safety of ENDS.

What do we know about explosions that occur with vapourisers?

There are continuing reports of reports of dramatic explosions occurring with ENDS from around the world. Those working in trauma care have published case-series of serious burns and injuries and shotgun like injuries arising from these explosions [e.g. Jiwani et al, 2017; Bohr S et al, 2016; Shastry S et al, 2016]

There are now dozens of cases reported in medical journals of burns and other injury related to lithium-ion battery powered device malfunction. Explosive malfunction causes

three complications: blast injury, thermal burn from the device and superheated vaping liquid and corrosive burn from lithium. (Brownson et al, 2016)

Broadly, device-related injuries can be grouped into those when the device is not in use, most commonly when in a trouser pocket, and when in use near or in the mouth. Explosions in the vicinity of the mouth during use are potentially catastrophic. Reported consequences include major dental injury (Brooks et al, 2017; Harrison et al, 2016), injury to soft tissues in the mouth and pharynx and even fractures of C1/C2 vertebrae (Norii and Plate, 2017).

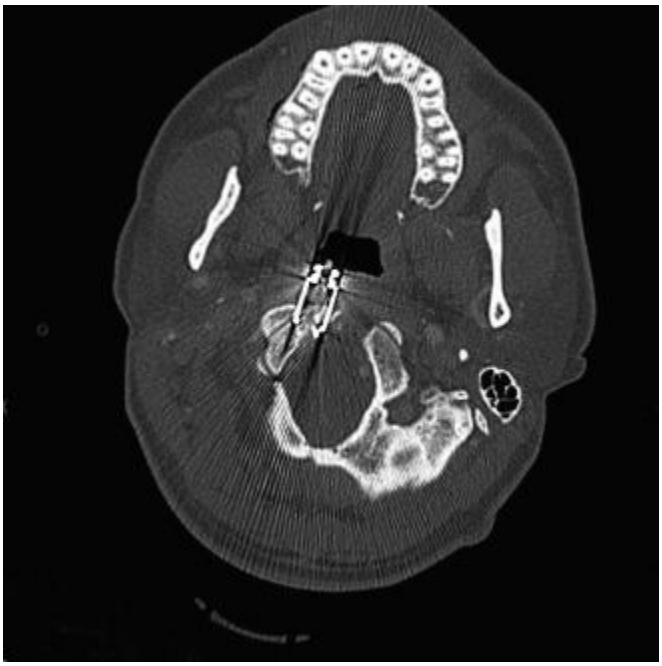

Image: Computed tomographic scan axial view showing fractures involving the superior cortex of the anterior arch of C1 at the posterior aspect of the foreign body. Source: Norri and Plate. Journal of Emergency Medicine, 2017. Volume 52, Issue 1, Pages 86–88.

Burn injuries are becoming so frequent that a classification system has been proposed (Patterson et al 2017) . Burns have most commonly been reported in the thigh area. Whereas first aid for thermal burn generally is based on water application, this may worsen the situation with lithium burn. The total burn area averages less than 10% but may include the external genitalia - an area that represents particular challenges for burns surgery and of course important long-term physical and psychological harms for the (generally) young person affected.

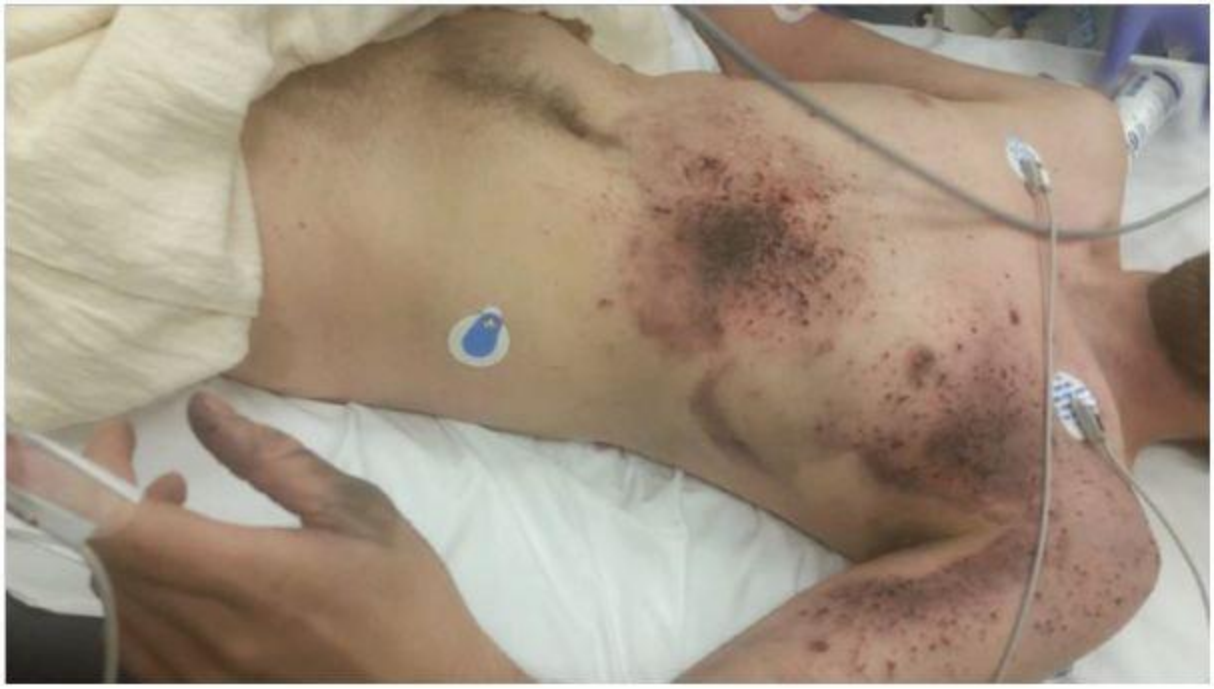

Image: Shrapnel-like injury from exploding ENDS device in a shirt pocket. Source: Shastry et al West J Emerg Med. 2016 Mar; 17(2): 177–180

ENDS advocates often note that other lithium battery-powered items like mobile phones and laptops have also exploded (often in far greater numbers than have ENDS), apparently implying from this that there is no need for concern about the safety of ENDS and their batteries. Explosions have occurred in pockets as well as during inhalation http://ecigone.com/featured/e-cigarette-explosions-comprehensive-list/

When mobile phones and computers explode, we see responsible industries suspend sales or enact global recalls, until they have rendered the product safe, as happened with the Samsung Galaxy Note 7 in 2016. At the time Samsung initiated its global recall, there had been only 35 cases of battery-related explosions - much less even than the number of cases of injury from exploding ENDS devices that have now been reported in medical journals alone.

In 2006, Dell computers recalled 4 million batteries (https://www.cnet.com/au/news/dell-to-recall-4-million-batteries/) and HP recalled 101,000 batteries in January 2017. We are very pleased that use of ENDS is banned on nearly every airline. There has been one report of an ENDS explosion and fire on board an aircraft (in an overhead locker) [http://www.star-telegram.com/news/local/community/fort-worth/article121150273.html]. Fortunately

this was extinguished by crew. An ENDS explosion in stowed luggage where it could not be extinguished could have catastrophic consequences.

The lack of regulatory standards for ENDS and their components stands in stark contrast to these other products.

Term of Reference #3. International approaches to legislating and regulating the use of E-cigarettes and personal vaporisers

Assertions have been made that there is widespread support for light touch regulation of ENDS, and that Australia is an outlier in its present policy position. This support is, however, far from universal among nations, health authorities and agencies. It is misleading to portray Australia as an outlier.

The "light touch" position is naturally favoured by those involved in ENDS manufacture and commerce, and accordingly is an approach supported by those conflicted with commercial objectives. It is also favoured by many who vape today.

Some experts have argued that that analysis of the International Tobacco Control Four Country surveys (i.e. data from the United States and Canada, the United Kingdom and Australia), demonstrate that:

> "Use of ECs in the real world during a quit attempt appears only effective for sustaining smoking abstinence in a less restrictive EC environment suggesting that the benefits of ECs [electronic cigarettes] for smoking cessation are likely highly dependent on the regulatory environment" [Yong et al, 2017].

This analysis has been strongly critiqued by Benmarhnia et al (2017), who identified that

> "there are at least three limitations in this paper that severely temper the conclusions reached by the authors and, in our view, cannot be addressed by the supporting data. Given the importance of the research question, it is equally important that firm conclusions be generated from appropriate data."

As they argued:

> "[firstly] . . the measurement of e-cigarette use was only valid in one of the ten waves of the data used" . . . secondly, that "the analyses suffer from inadequate sample size, drawing into question the generalizability of the sample to the population they are purported to represent. For instance, there are only 50 respondents from either Canada or Australia who reported using an e-cigarette over the entire 11-year period" . . . and thirdly, that "the authors consider how the association of e-cigarette use with 30-day cigarette abstinence varies across countries categorized according to their regulatory environment . . . , but the validity

of this proposed singular distinction has not been demonstrated" [Benmarhnia et al, 2017]

The Johns Hopkins Bloomberg School of Public Health has summarised ENDS regulation of 123 countries in a comprehensive website (see http://globaltobaccocontrol.org/node/14052). This summary reported that the sale of all types of ENDS is banned in 26 countries, 18 countries regulate ENDS as medicinal products, 26 countries regulate ENDS as tobacco products (or imitation/derivative/substitute products) and four countries regulate ENDS containing nicotine as poisons. Use of ENDS is banned in three countries (Cambodia, Jordan and the United Arab Emirates). As of February 2016, 71 countries had been identified that regulate ENDS.

Global

Among leading health agencies with strong concerns about ENDS are the World Health Organization, the US Surgeon General, the, the US FDA,, Australia's National Health and Medical Research Council and the TGA.

USA

- US Food and Drug Administration (see regulations here https://www.fda.gov/tobaccoproducts/labeling/productsingredientscomponents/ucm456610.htm#regulation)

- US Surgeon General (see https://e-cigarettes.surgeongeneral.gov/documents/2016_sgr_full_report_non-508.pdf)
-

Thes 51 US groups listed below have all urged the US political administration to support the Food and Drug Administration's regulation of ENDS (see http://www.tobaccofreekids.org/press_releases/post/2017_05_17_fda)

Action on Smoking & Health
American Academy of Family Physicians
American Academy of Oral and Maxillofacial Pathology
American Academy of Pediatrics
American Association for Cancer Research
American Association for Dental Research
American Association for Respiratory Care
American Cancer Society Cancer Action Network
American College of Cardiology
American College of Occupational and Environmental Medicine

American College of Physicians
American College of Preventive Medicine
American Congress of Obstetricians and Gynecologists
American Dental Association
American Heart Association
American Lung Association
American Medical Association
American Psychological Association
American Public Health Association
American School Health Association
American Society of Addiction Medicine
American Society of Clinical Oncology
American Thoracic Society
Americans for Nonsmokers' Rights
Asian Pacific Partners for Empowerment, Advocacy and Leadership
Association of Women's Health, Obstetric & Neonatal Nurses
Big Cities Health Coalition
Campaign for Tobacco-Free Kids
ClearWay Minnesota
Community Anti-Drug Coalitions of America
Eta Sigma Gamma - National Health Education Honorary
March of Dimes
National African American Tobacco Prevention Network
National Association of County and City Health Officials
National Association of Pediatric Nurse Practitioners
National Center for Health Research
National Hispanic Medical Association
National Network of Public Health Institutes
National Physicians Alliance
Oncology Nursing Society
Prevention Institute
Prevention Partners
Public Health Solutions
Society for Cardiovascular Angiography and Interventions
Society for Public Health Education
Students Against Destructive Decisions
The Society of State Leaders of Health and Physical Education
Tobacco Control Legal Consortium
Trust for America's Health
Truth Initiative

United Methodist Church- General Board of Church and Society

Australia

In Australia, the NHMRC, the Cancer Council, the Heart Foundation, the Australian Medical Association, Lung Foundation Australia, Thoracic Society of Australia and New Zealand and the Public Health Association of Australia and New Zealand have all expressed support for TGA regulation of ENDS.

UK

The Public Health England agency claims there is a consensus in England regarding the safety and usefulness of ENDS. This ignores the fact that prominent health organisations and scientists within the UK are not part of it, and have demonstrably disagreed with at least some of PHE's position. For example:

1. The British Heart Foundation: "There is a lack of empirical research regarding the effectiveness of e-cigarettes as a smoking cessation aid . . .". [https://www.bhf.org.uk/publications/policy-documents/e-cigarettes-policy-statement
2. Public Health Wales: "Confectionery-like' flavours of e-liquid should not be permitted, in order to reduce the appeal of ENDS to children and young people". [http://www.wales.nhs.uk/sitesplus/888/news/43873]
3. ASH Scotland e.g. ". . . widely varying estimates demonstrate the difficulty of attributing a meaningful value to {the health} risk {of e-cigarettes} without long-term studies of health of e-cig users." (http://www.ashscotland.org.uk/media/627028/e-cigarettes-march-2017.pdf
4. Professor Helen Stokes-Lampard, Chair of the Royal College of General Practitioners "Vaping should not be allowed in public places where cigarette smoking is banned". (http://www.rcgp.org.uk/news/2016/december/vaping-should-not-be-allowed-in-public-places-where-cigarette-smoking-is-banned-says-rcgp-chair.aspx)
5. The British Medical Association: "There is some evidence in other countries that e-cigarettes may be acting as a gateway to smoking" http://www.bma.org.uk/-/media/files/pdfs/working%20for%20change/policy%20and%20lobbying/pa-e-cigarettesbriefing-03-12-2014.pdf (see Term of Ref 5 below)
6. The Royal Pharmaceutical Society: "We have expressed concern over possible safety issues of using e-cigarettes, as well as a lack of evidence of their efficacy when used for smoking cessation" . . . "We recommend that policy-makers must do everything they can to avoid a new generation of people becoming addicted to nicotine. This is particularly important in light of the current lack of evidence in relation to long-term health effects of using e-cigarettes, and their secondhand emissions" (https://www.rpharms.com/making-a-difference/policy-a-z/e-cigarettes)

7. English toxicologists Dr Robert Combes and Emeritus Professor Michael Balls' comprehensive critique of the position of Public Health England is self-explanatory [Combes & Balls, 2015].

Seven policy approaches to ENDS regulation were outlined in Section 4 of a report prepared for the Commonwealth Department of Health in 2016 (the Committee secretariat has been sent a copy).
These policy approaches are not meant to be mutually exclusive.

The seven possible policy approaches are as follows:
Policy approach 1: Maintain the status quo
Policy Approach 2: Increase awareness and enforcement of and compliance with existing legislation
Policy approach 3: Regulate ENDS as medicines
Policy approach 4: Regulate ENDS as tobacco products
Policy approach 5: Regulate ENDS as consumer products
Policy approach 6: Develop an ENDS regulatory framework
Policy approach 7: Adopt measures to ban ENDS

We commend that report for the Committee's consideration (Note: author Chapman contributed a section to that report)

Term of Reference #4: The appropriate regulatory framework for E-cigarettes and personal vaporisers in Australia

Australia introduced modern approaches to drug regulation in 1963 following the thalidomide tragedy. The Therapeutic Goods Administration (TGA) and its predecessors have had responsibility for the evaluation, regulation and scheduling of any product where therapeutic claims are made.

The TGA

> " safeguards and enhances the health of the Australian community through effective and timely regulation of therapeutic goods". It is well recognised as a crucial and meticulous component of Australia's health system. Its activities include "ensuring that therapeutic goods available for supply in Australia are safe and fit for their intended purpose". The full role and approaches taken by the TGA are set out on the TGA website (https://www.tga.gov.au/)

We have consistently argued that ENDS should remain subject to the TGA process. Nobody could take seriously any suggestion that they are not being promoted as cessation aids. There is simply no worthwhile case for bypassing the TGA other than that some groups or individuals may not be comfortable with the outcomes of rigorous, objective scientific review.

Further, bypassing the TGA on the basis of lobbying by sectional interests would set a potentially disastrous precedent, indicating a lack of confidence in the TGA and opening the door to similar lobbying and bypassing for many other products where companies or individuals wish to avoid proper scrutiny.

Quack claims about alleged cures for deadly and common diseases like cancers, HIV/AIDS and asthma have long been with us. But we do not allow those with an alleged cancer cure to by-pass the TGA assessment process and sell and promote a substance as cancer-curing simply on the strength of either commercial lobbying or emotional rhetoric.

We are aware of an argument that if ENDS makers had to convince the TGA on safety and effectiveness, only the pharmaceutical and tobacco industries could afford to conduct the research to the standards required. This in itself is open to debate. But the alternative -- to allow any backyard "kitchen chemist" maker of vaping equipment and ingredients to sell

and promote their products without TGA regulation – is an irresponsible proposal that would both put the health of consumers at risk and set a very dangerous precedent.

As noted in an article in the Medical Journal of Australia co-authored by McKee, Chapman and Daube:

> "In Australia, anyone considering importing or supplying e-cigarettes as a cessation aid must submit an application to the Therapeutic Goods Administration (TGA) with evidence of their safety and efficacy. The TGA then considers the evidence before determining whether the product may be sold, and, if so, under what conditions." [McKee, Chapman & Daube, 2016]

This is the approach that should be taken in relation to ENDS. It may be important to stress in this context that our position is not, as has sometimes been falsely stated, simple "opposition" to new approaches. It is that proper processes should be followed; the role of the TGA should be supported; and any determinations by the TGA should be respected.

In 2016-17 the TGA considered proposals to bypass poison controls to enable access to liquid nicotine for vaping. Following extensive consultations, submissions and reviews the TGA concluded that "the scheduling for nicotine remains appropriate". (see https://www.tga.gov.au/book-page/21-nicotine-0)The TGA comments and final decisions set out a wide range of concerns and conclusions leading to this decision, including those summarised under the headings "Delegates' interim decision" and "Delegates' final decision". We recognise that some who make submissions to the Inquiry may not like the verdict of this impartial and authoritative referee, but we urge the Committee to recognise, support and uphold the integrity and authority of the TGA.

It is further relevant to note that the nation's highest medical authority, the National Health and Medical Research Council, has also carefully reviewed the evidence on e-cigarettes/ENDS, with two CEO statements, first in 2015, then an updated statement as recently as April 2017. The 2017 statement reports that while "Electronic cigarettes (e-cigarettes, also known as electronic nicotine delivery systems (ENDS) or electronic non-nicotine delivery systems (ENNDS)) are often marketed as a method to assist smokers to quit, or as a 'safe alternative' to conventional tobacco cigarettes", ".....there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed".

We recognise that, as in relation to the TGA, some groups or individuals may not be comfortable with the outcomes of rigorous, objective scientific review, but that should not be allowed to undermine the authority of the NHMRC or its advice, any more than this

should occur on the basis of representations from commercial interests or enthusiasts in any other area.

Refusing to accept the umpire's decision

Indeed, we find it disturbing that there are clearly some who wish to bypass both the TGA and NHMRC despite the crucial role both these bodies play in ensuring that Australian governments and community receive the best possible advice, and that the health of the public is well protected, with appropriate safeguards.

The TGA is in every sense Australia's national "umpire" on claims about therapeutic product safety and efficacy. Its processes and decisions over decades have given Australia one of the world's best and most envied therapeutic regulatory systems. Those who have been working to try and have the TGA circumvented as this umpire are challenging its authority on the flimsiest of pretexts. They have refused to accept the TGA umpire's decision, a course of action which brings them great discredit.

Many of those who have been prominent in this exercise have little if any serious track record or experience in population-focussed tobacco control. They, and some from overseas, may not be aware of the roles and critical importance of the TGA and NHMRC.

ENDS use in Australia today: very low

In considering policy options for ENDS, the we believe that the Committee should be mindful of the size of the likely demand for ENDS, and also of the potential risks of ENDS becoming popular with Australian children and young people should their accessibility and promotion move in the directions being advocated by the ENDS and tobacco industries.

ENDS are widely available for sale in Australia, although e-juice containing nicotine must be imported. This is very easily done (as easily as ordering books, clothing or other consumer goods is today on-line). Despite this, ENDS use is a very marginal activity in Australia today. The AIHW 2013 national survey (the largest survey on smoking and ENDS use available for Australia) reported that:

Year	Ever used e-cigarettes	Among daily smokers
2013	4.5% of all persons 1.8% of 14+ non-smokers 18.8% of 14+ smokers	

2016	8.8% of all persons 4.9% of 14+ non-smokers 31% of 14+ smokers	**A. Of smokers** 1.5% of daily smokers 1.2% of at least weekly smokers 0.7% of at least monthly smokers 1.0% of less than monthly smokers 6.8% used to use, but no longer do 19.9% tried it once or twice 69% never tried B. 0.8% **of ex-smokers**

Source: **http://www.aihw.gov.au/alcohol-and-other-drugs/data-sources/ndshs-2016/data/** (from Tables 8 & 9)

12.2% of the Australian population aged 14 years and over smoke daily. Yet only 1.5% of these are vaping daily (ie 0.186% of all Australians aged 14 and over). It is *far* more common (17.8 times more common) for daily smokers to have experimented with or used and then stopped using ENDS than for daily smokers to be using them today.

Only 0.8% of ex-smokers are vaping. We do not know what proportion of these are recent smokers who quit and are now vaping, and what proportion may be longer term ex-smokers who took up vaping long after quitting.

There are two main Australian on-line forums for vapers; Aussie vapers (http://forums.aussievapers.com/forum.php with 1,781 active members as at 26 June, 2017 and Vaper Cafe www.vapercafeaustralia.com/ with only 931 members on the same date. Many members belong to both. It is not known how many of these are Australian members and how many are from abroad.

These numbers provide no evidence that anything other than transient curiosity vaping is widespread in Australia. By far the largest numbers of people who have vaped are smokers who have tried it a few times and did not then go on to vape regularly (some 20% of smokers). There is no evidence that there are large numbers of smokers in Australia who want to vape but cannot do so, given the ease with which those who are vaping now are able to obtain both vaping equipment and nicotine containing e-juice.

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Term of Reference #5. Any other related matter

Two issues deserve the Committee's careful attention.

Does ENDS use predict later uptake of smoking?

Earlier, we were critical of claims made by those involved in ENDS manufacture and commerce that they had no interest in seeing children use ENDS. We argued that this is a commercially disingenuous claim, made entirely for public relations purposes. No industry concerned for its longevity would claim that it had no interest in fomenting strong interest in its products among future users.

Australia currently has the lowest rate of smoking among children ever recorded in this country. Only 2% of Australian children and young people aged 12-17 have ever smoked 100 or more cigarettes (see http://www.aihw.gov.au/2016-national-drug-strategy-household-survey/).
This is the lowest level ever recorded and is a huge testimony to the effectiveness of Australian tobacco control over the decades. Given that there is no evidence of any significant use of nicotine replacement therapy among youth, we are confident that regular exposure to nicotine in any form is fast becoming a thing of the past among Australian youth.

This is disastrous news for both tobacco companies and ENDS companies alike. With the former, the search for acceptable routes into nicotine addiction that might see young ENDS users also start smoking would be front of mind.

Appendix 3 is a Powerpoint presentation of evidence prepared by a colleague, A/Prof Stacey Carter, found in tobacco industry documents, about their intense interest in children and the duplicitous efforts they took to publicly deny that interest. All companies will have done elementary calculations about the need to attract starters among young people to expand the user base. Why contain the appeal of ENDS just to the dwindling number of smokers when the prospects of interesting the far more numerous non-smokers beckon?

ENDS as presursor or catalyst to smoking
As at February 2017, there were nine longitudinal studies suggesting that children starting nicotine use with ENDS and transitioning to smoking conventional cigarettes [Soneji et al, 2017]. These studies all considered youth who had not smoked a conventional cigarette, and then compared smoking between youth who did and did not use ENDS at baseline.

Critics of these studies often dismiss them by saying that all they show is that "children who are going to smoke in the future, will smoke in the future". They argue that all these studies do is show that those children likely to become smokers are do so. However, such studies do attempt to control for relevant confounders:

> "They [the critics] miss the fact that the studies controlled for variables that are defining characteristics of high-risk youth, including risk-taking, impulsiveness, negative affect, low parental support, and affiliation with deviant peers, and the effect of e-cigarette use for smoking onset was independent of these confounders. Moreover, recent research with different designs has shown that e-cigarettes are most strongly related to smoking onset among lower-risk adolescents, thus specifically contradicting the confounding hypothesis." (Wills, 2017)

The extent of this gateway or catalytic effect of initial ENDS use on later smoking uptake has now been shown in a meta-analysis of all these studies, appropriately adjusting and allowing for demographic, psychosocial, and behavioral risk factors for cigarette smoking, found that the odds of subsequent cigarette smoking were quadrupled among e-cigarette users [Soneji et al, 2017]. E-cigarette users are 5 times more likely to smoke but this is reduced to *only* a three-fold increased risk after adjusting for the relevant confounding factors typically highlighted by critics. Unless critics of these findings propose another confounding factor to which they have not previously alluded the Soneji et al evidence is compelling.

These findings and opinions further substantiate the concerns raised regarding the use of electronic cigarettes by youth and young adults in the US by the Surgeon General in late 2016, a comprehensive scientific report, generated from the input of approximately 150 experts in this field [US Surgeon General, 2016].

We are completely unimpressed the with the circularity of the response often made by ENDS advocates to findings about the possibility that ENDS use may act as a catalyst to subsequent smoking. A typical glib reply is that "kids who are going to try stuff, try stuff" made to any suggestion of vaping being an important predisposer to smoking. Here, they act as if the possibility that we may ever identify critical factors other than a circular "those who will smoke, will smoke" insight that increase the probability of someone taking up smoking is somehow preposterous.

We have had no problem with research that has often identified factors that promote smoking uptake and which governments then try to influence with policy or programs (eg: low price, tobacco advertising, parental smoking, smoking by teachers, etc.). But when

research suggests that using ENDS might condition some children into thinking "I wonder what the 'real thing' [ie smoking] is like?", we see some extraordinary responses.

Professor Peter Hajek, a long time advocate of ENDS, has said about the Soneji et al meta-analysis:

> "People who drink white wine are more likely to also try red wine than teetotallers, but common sense would not suggest that this means that removing the white will reduce the drinking of the red."

(http://www.sciencemediacentre.org/expert-reaction-to-review-of-e-cigarettes-and-smoking-in-young-adults/)

This is an inept analogy, as one of the authors of the *JAMA* meta-analysis exposed with the following salient point.

> "Young people report that there is a lot of pressure among e-cigarette only users to smoke a 'real' cigarette. It may be somewhat analogous to the fact that teens who use flavored alcohol are often pressured socially to step up their game to harder forms of alcohol." (see https://www.reuters.com/article/us-health-teens-vaping-idUSKBN19H292)

ENDS, with their many teen-friendly flavours, their less harsh "throat grab", the ease with which they can be used inconspicuously (little smell, rapidly secretable), and their hyped "almost totally safe' propaganda have considerable appeal to youth compared with smoking. But, just as a large proportion of adults who experiment with ENDS do not continue using them, finding them unsatisfying [eg:Pepper et al 2014] so too it is likely that some young people may move on to cigarettes, with ENDS abandoned as "training wheels".

Schneider & Diehl (2015) considered the inadequacies of crude "gateway" hypotheses and posited a compelling "catalyst" model for researchers and policy makers to consider about how initial ENDS use may stimulate later smoking. Their

> "results indicate that the perceived health risks, specific product characteristics (such as taste, price and inconspicuous use), and higher levels of acceptance among peers and others potentially make e-cigarettes initially more attractive to adolescents than tobacco cigarettes. Later, increasing familiarity with nicotine could lead to the reevaluation of both electronic and tobacco cigarettes and subsequently to a potential transition to tobacco smoking."

ENDS advocates have pointed out that cross-sectional surveys of smoking in the USA and England show that as ENDS use is rising, smoking prevalence is falling in adolescents. From this, they imply that there therefore cannot be any significant problem of ENDS use causing an increase in smoking among youth. But this does not follow at all.

There are multiple reasons for both the rise and the fall in smoking prevalence. If the impact of all factors driving smoking down in youth is greater than the impact of any putative ENDS "gateway" effect on smoking, smoking prevalence among youth would be falling.

But such a fall could nonetheless mask considerable smoking uptake caused by any ENDS gateway effects that were not widespread enough to stop the net fall in smoking prevalence still occurring. For this reason, longitudinal cohort studies such as those meta-analysed by Soneji et al (2017) are critical in understanding whether ENDS are an important catalyst for smoking among youth. As we have emphasised, that analysis shows that E-cigarette users are 5 times more likely to smoke but this is reduced to *only* a three-fold increased risk after adjusting for the relevant confounding factors typically highlighted by critics.

Should restrictions be placed on where vaping can occur?

Policy on smoking in public spaces is a state and territory matter, so beyond the remit of this Committee, other than in locations controlled by Commonwealth law such as some airports. In Appendix 4 [Chapman, Daube, Maziak, 2017] , we set out several reasons why ENDS use should not be allowed in any setting where cigarette smoking is not allowed. These include:

- Exposure of the public to harmful particles, particularly in enclosed environments with high concentration of persons vaping (see this video https://www.youtube.com/watch?v=VxiEZeFE2Zs and the Figure below
- Risks of catastrophic explosions (especially on aircraft -- see earlier)
- Triggering relapse in former smokers
- Renormalisaing the smoking "performance"

Both the American Indoor Hygiene Association's 2014 *White Paper: Electronic Cigarettes in the Indoor Environment*, subsequent to their full independent scientific review here https://www.aiha.org/government-affairs/PositionStatements/Electronc%20Cig%20Document_Final.pdf and the American Society of Heating Refrigeration and Air-conditioning Engineers 2016 *Standards 62.1 & 62.2; The Standards for Ventilation and Indoor Air Quality* here https://www.ashrae.org/resources--publications/bookstore/standards-62-1--62-2 confirm that there are potential health risks and concerns related to bystanders and passive vaping in indoor public areas, especially for susceptible groups such as the old and young, those with pre-existing health issues e.g. cardiac and respiratory, pregnant mothers. They strongly recommend that e-cigarettes should be treated the same as conventional cigarettes in such areas. The American Indoor Hygiene Association stated that:

> "e-cigarettes are not emission-free and that their pollutants could be of health concern for users and those who are exposed secondhand. … [T]heir use in the indoor environment should be restricted, consistent with current smoking bans, until and unless research documents that they will not significantly increase the risk of adverse health effects to room occupants" [AIHA, 2014].

Data confirm the need for this precautionary policy standpoint, showing that levels of fine particulate matter ($PM_{2.5}$) in a large hotel event room (4023 m^3) increased from 2-3 $\mu g/m^3$

to as high as 819 μg/m^3 μg/m^3 (interquartile range: 761-975 μg/m^3) when 59 to 86 people were using their e-cigarettes (Soule et al, 2017): a level comparable to a very smoky bar or casino. These levels substantially exceeded the US Environmental Protection Agency annual time-weighted standard for $PM_{2.5}$ of 12μg/m^3.

Tangentially, It has been argued by Bauld et al (2016) that

> "if and when vapour products with a medicinal license become available, it will be important to allow their use indoors, just as asthma inhalers, which dispense a drug and propellants into the atmosphere, can be used indoors."

The comparison and conclusion here is fundamentally inappropriate, and misleading. Newman et al showed, as long ago as 1991, that the amount of dosed drug exhaled by asthmatics using inhalers ranged from just 0.2%-1.7% across different puffing behaviours [Newman et al, 1991]. A typical person who uses an asthma reliever therapy puffer e.g. Salbutamol 100mcg would not normally be recommended to use it more than 2 puffs four times a day (8 puffs/day), as the UK National Institute for Health and Clinical Excellence recommend the prescription of salbutamol, with reference to British National Formulary (https://bnf.nice.org.uk/drug/salbutamol.html#indicationsAndDoses). Conversely, vapers can take up to, and therefore exhale, 610 puffs a day, with an average of around 200 puffs [Martin et al, 2016].

There is simply no comparison between what the asthma medication and propellant, and what one or even a few asthmatics might exhale into, for example, a crowded bar over a few hours, and what potentially dozens of vapers could generate in the sort of exuberant cloud chasing sessions that vaping in bars can entail. Furthermore, unlike vapers, asthmatics obviously do not participate in asthma puffer social events and competitions.

In conclusion:

Smoking remains Australia's largest single preventable cause of death and disease.

Trends among adults and children in Australia have been encouraging over time as a result of consensus action based on recommendations from health authorities. As a consequence, Australia is one of the world's leading countries in reducing smoking in adults and onset of smoking among children and young people. It is especially encouraging that 98% of those aged 12 – 17 are classified as never-smokers.

There is a strong evidence base for action that will further reduce smoking and its harms in both the community as a whole and disadvantaged groups.

There should be caution about introducing new products, with inevitable consequent promotion, that may distract from further evidence-based action, introduce new risks to the community, and undermine the progress that has been made.

The evidence supporting e-cigarettes as a cessation aid is weak; there is some evidence that they may be counter-productive; and there are significant concerns about potential harms that may arise from use of e-cigarettes and related products, including renormalising smoking behaviour and acting as a catalyst for smoking among children and young people. There is further concern at the enormous range of products and flavours being developed and promoted, with lack of information as to their consequences.

Leading health authorities such as the World Health Organization and the US Surgeon General have supported the case for a cautionary approach, which has also been adopted by many other countries.

The National Health and Medical Research Council (NHMRC) has recently concluded that "there is currently insufficient evidence to support claims that e-cigarettes are safe and further research is needed to enable the long-term safety, quality and efficacy of e-cigarettes to be assessed". The Therapeutic Goods Administration (TGA) has also recently concluded that "unlike Nicotine Replacement Therapy (NRT) products, which have been rigorously assessed for efficacy and safety and, therefore, approved by the Therapeutic Goods Administration for use as aids in the withdrawal from smoking, no assessment of electronic cigarettes has been undertaken and, therefore, the quality and safety of electronic cigarettes is not known."

E-cigarettes, as any other products claimed or promoted as therapeutic products to help smokers quit or reduce their harms should remain subject to the processes of the TGA, whose role, independence and integrity should be strongly supported, as should that of the NHMRC.

Recognising Article 5.3 of the WHO Framework Convention on Tobacco Control, to which the Australian Government is a signatory, any considerations on this issue should be protected from direct or indirect influences by commercial and other vested interests of the tobacco industry.

Appendix 1: Recent publications reporting findings about potential harm of exposure to e-cigarettes

Electronic cigarette aerosols suppress cellular antioxidant defenses and induce significant oxidative DNA damage.

Ganapathy V, Manyanga J, Brame L, McGuire D, Sadhasivam B, Floyd E, Rubenstein DA, Ramachandran I, Wagener T, Queimado L.

PLoS One. 2017 May 18;12(5):e0177780. doi: 10.1371/journal.pone.0177780.

BACKGROUND:

Electronic cigarette (EC) aerosols contain unique compounds in addition to toxicants and carcinogens traditionally found in tobacco smoke. Studies are warranted to understand the public health risks of ECs.

OBJECTIVE:

The aim of this study was to determine the genotoxicity and the mechanisms induced by EC aerosol extracts on human oral and lung epithelial cells.

METHODS:

Cells were exposed to EC aerosol or mainstream smoke extracts and DNA damage was measured using the primer anchored DNA damage detection assay (q-PADDA) and 8-oxo-dG ELISA assay. Cell viability, reactive oxygen species (ROS) and total antioxidant capacity (TAC) were measured using standard methods. mRNA and protein expression were evaluated by RT-PCR and western blot, respectively.

RESULTS:

EC aerosol extracts induced DNA damage in a dose-dependent manner, but independently of nicotine concentration. Overall, EC aerosol extracts induced significantly less DNA damage than mainstream smoke extracts, as measured by q-PADDA. However, the levels of oxidative DNA damage, as indicated by the presence of 8-oxo-dG, a highly mutagenic DNA lesion, were similar or slightly higher after exposure to EC aerosol compared to mainstream smoke extracts. Mechanistically, while exposure to EC extracts significantly increased ROS, it decreased TAC as well as the expression of 8-oxoguanine DNA glycosylase (OGG1), an enzyme essential for the removal of oxidative DNA damage.

CONCLUSIONS:

Exposure to EC aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage. These findings emphasize the urgent need to investigate the potential long-term cancer risk of exposure to EC aerosol for vapers and the general public.

E-cigarettes induce toxicological effects that can raise the cancer risk.

Canistro D, Vivarelli F, Cirillo S, Babot Marquillas C, Buschini A, Lazzaretti M, Marchi L, Cardenia V, Rodriguez-Estrada MT, Lodovici M, Cipriani C, Lorenzini A, Croco E, Marchionni S, Franchi P, Lucarini M, Longo V, Della Croce CM, Vornoli A, Colacci A, Vaccari M, Sapone A, Paolini M.

Sci Rep. 2017 May 17;7(1):2028. doi: 10.1038/s41598-017-02317-8.

Abstract

BACKGROUND:

Electronic cigarette (EC) aerosols contain unique compounds in addition to toxicants and carcinogens traditionally found in tobacco smoke. Studies are warranted to understand the public health risks of ECs.

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CONCLUSIONS:

Exposure to EC aerosol extracts suppressed the cellular antioxidant defenses and led to significant DNA damage. These findings emphasize the urgent need to investigate the potential long-term cancer risk of exposure to EC aerosol for vapers and the general public.

Benzene formation in electronic cigarettes.
Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM, Duell AK, Peyton DH.
PLoS One. 2017 Mar 8;12(3):e0173055. doi: 10.1371/journal.pone.0173055.

Abstract

BACKGROUND/OBJECTIVE:
The heating of the fluids used in electronic cigarettes ("e-cigarettes") used to create "vaping" aerosols is capable of causing a wide range of degradation reaction products. We investigated formation of benzene (an important human carcinogen) from e-cigarette fluids containing propylene glycol (PG), glycerol (GL), benzoic acid, the flavor chemical benzaldehyde, and nicotine.

METHODS/MAIN RESULTS:
Three e-cigarette devices were used: the JUULTM "pod" system (provides no user accessible settings other than flavor cartridge choice), and two refill tank systems that allowed a range of user accessible power settings. Benzene in the e-cigarette aerosols was determined by gas chromatography/mass spectrometry. Benzene formation was ND (not detected) in the JUUL system. In the two tank systems benzene was found to form from propylene glycol (PG) and glycerol (GL), and from the additives benzoic acid and benzaldehyde, especially at high power settings. With 50:50 PG+GL, for tank device 1 at 6W and 13W, the formed benzene concentrations were 1.9 and 750 μg/m3. For tank device 2, at 6W and 25W, the formed concentrations were ND and 1.8 μg/m3. With benzoic acid and benzaldehyde at ~10 mg/mL, for tank device 1, values at 13W were as high as 5000 μg/m3. For tank device 2 at 25W, all values were ≤~100 μg/m3. These values may be compared with what can be expected in a conventional (tobacco) cigarette, namely 200,000 μg/m3. Thus, the risks from benzene will be lower from e-cigarettes than from conventional cigarettes. However, ambient benzene air concentrations in the U.S. have typically been 1 μg/m3, so that benzene has been named the largest single known cancer-risk air toxic in the U.S. For non-smokers, chronically repeated exposure to benzene from e-cigarettes at levels such as 100 or higher μg/m3 will not be of negligible risk.

E-cigarettes as a source of toxic and potentially carcinogenic metals.
Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM.
Environ Res. 2017 Jan;152:221-225. doi: 10.1016/j.envres.2016.09.026.

Abstract

BACKGROUND AND AIMS:

The popularity of electronic cigarette devices is growing worldwide. The health impact of e-cigarette use, however, remains unclear. E-cigarettes are marketed as a safer alternative to cigarettes. The aim of this research was the characterization and quantification of toxic metal concentrations in five, nationally popular brands of cig-a-like e-cigarettes.

METHODS:

We analyzed the cartomizer liquid in 10 cartomizer refills for each of five brands by Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

RESULTS:

All of the tested metals (cadmium, chromium, lead, manganese and nickel) were found in the e-liquids analyzed. Across all analyzed brands, mean (SD) concentrations ranged from 4.89 (0.893) to 1970 (1540) μg/L for lead, 53.9 (6.95) to 2110 (5220) μg/L for chromium and 58.7 (22.4) to 22,600 (24,400) μg/L for nickel. Manganese concentrations ranged from 28.7 (9.79) to 6910.2 (12,200) μg/L. We found marked variability in nickel and chromium concentration within and between brands, which may come from heating elements.

CONCLUSION:

Additional research is needed to evaluate whether e-cigarettes represent a relevant exposure pathway for toxic metals in users.

Detection of 5-hydroxymethylfurfural and furfural in the aerosol of electronic cigarettes.
Soussy S, El-Hellani A, Baalbaki R, Salman R, Shihadeh A, Saliba NA.
Tob Control. 2016 Nov;25(Suppl 2):ii88-ii93. doi: 10.1136/tobaccocontrol-2016-053220.

Abstract

SIGNIFICANCE:

The wide availability of sweet flavours has been hypothesised as a factor in the popularity of electronic cigarette (ECIG), especially among youth. Saccharides, which are commonly used to impart a sweet flavour to ECIG liquids, thermally degrade to produce toxic compounds, like aldehydes and furans. This study investigates the formation of furanic compounds in aerosols when ECIG liquid solutions of varying sweetener concentrations are vaped under different power and puff duration.

METHODS:

Liquids are prepared by mixing aqueous sucrose, glucose or sorbitol solutions to a 70/30 propylene glycol/glycerin solution. Aerosols are generated and trapped on filter pads using a commercially available ECIG operating at 4.3 and 10.8 W and 4 and 8 s puff duration. Extraction, elimination of matrix interference and quantification are achieved using novel

solid phase extraction and gas chromatography tandem mass spectrometry methods (GC-MS).

RESULTS:

Well-resolved GC peaks of 5-hydroxymethylfurfural (HMF) and furfural (FA) are detected. Both HMF and FA are quantified in the aerosols of sweet-flavoured e-liquids under various vaping conditions. Levels of furan emissions are significantly correlated with electric power and sweetener concentration and not with puff duration. Unlike saccharides, the formation of HMF and FA from a sugar alcohol is negligible.

CONCLUSIONS:

The addition of sweeteners to ECIG liquids exposes ECIG user to furans, a toxic class of compounds. Under certain conditions, the per-puff yield of HMF and FA in ECIG emissions is comparable to values reported for combustible cigarettes.

Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics.

El-Hellani A, Salman R, El-Hage R, Talih S, Malek N, Baalbaki R, Karaoghlanian N, Nakkash R, Shihadeh A, Saliba NA.

Nicotine Tob Res. 2016 Oct 7. pii: ntw280

Abstract

INTRODUCTION:

Available in hundreds of device designs and thousands of flavors, electronic cigarette (ECIG) may have differing toxicant emission characteristics. This study assesses nicotine and carbonyl yields in the most popular brands in the U.S. market. These products included disposable, prefilled cartridge, and tank-based ECIGs.

METHODS:

Twenty-seven ECIG products of 10 brands were procured and their power outputs were measured. The e-liquids were characterized for pH, nicotine concentration, propylene glycol/vegetable glycerin (PG/VG) ratio, and water content. Aerosols were generated using a puffing machine and nicotine and carbonyls were, respectively, quantified using gas chromatograph and high-performance liquid chromatography. A multiregression model was used to interpret the data.

RESULTS:

Nicotine yields varied from 0.27 to 2.91 mg/15 puffs, a range corresponding to the nicotine yield of less than 1 to more than 3 combustible cigarettes. Nicotine yield was highly correlated with ECIG type and brand, liquid nicotine concentration, and PG/VG ratio, and to a lower significance with electrical power, but not with pH and water content. Carbonyls, including the carcinogen formaldehyde, were detected in all ECIG aerosols, with total carbonyl concentrations ranging from 3.72 to 48.85 µg/15 puffs. Unlike nicotine, carbonyl concentrations were mainly correlated with power.

CONCLUSION:

In 15 puffs, some ECIG devices emit nicotine quantities that exceed those of tobacco cigarettes. Nicotine emissions vary widely across products but carbonyl emissions showed little variations. In spite of that ECIG users are exposed to toxicologically significant levels of carbonyl compounds, especially formaldehyde. Regression analysis showed the importance of design and e-liquid characteristics as determinants of nicotine and carbonyl emissions.

IMPLICATIONS:

Periodic surveying of characteristics of ECIG products available in the marketplace is valuable for understanding population-wide changes in ECIG use patterns over time.

Respiratory bronchiolitis-associated interstitial lung disease secondary to electronic nicotine delivery system use confirmed with open lung biopsy.

Flower M, Nandakumar L, Singh M, Wyld D, Windsor M, Fielding D.

Respirol Case Rep. 2017 Apr 3;5(3):e00230. doi: 10.1002/rcr2.230. eCollection 2017 May.

Abstract

As a modern phenomenon, there is currently limited understanding of the possible toxic effects and broader implications of electronic nicotine delivery systems (ENDS). Large volumes of aerosolized particles are inhaled during "vaping" and there are now an increasing number of case reports demonstrating toxic effects of ENDS, as well as human studies demonstrating impaired lung function in users. This article presents a case of respiratory bronchiolitis interstitial lung disease (RB-ILD) precipitated by vaping in a 33-year-old male with 10 pack years of traditional cigarette and prior treatment for mixed germ cell tumour. The patient had started vaping 10-15 times per day while continuing to smoke 10 traditional cigarettes per day. After 3 months of exposure to e-cigarette vapour, chest computed tomography demonstrated multiple new poorly defined pulmonary nodules with fluffy parenchyma opacification centred along the terminal bronchovascular units. Video-assisted thoracoscopy with lung biopsy of the right upper and right middle lobes was undertaken. The microscopic findings were overall consistent with RB-ILD. This

case demonstrates toxicity with use of ENDS on open lung biopsy with resolution of radiographic findings on cessation. We believe that this is the first case where open lung biopsy has demonstrated this and our findings are consistent with RB-ILD.

Cytotoxic and Genotoxic Effects of Electronic Cigarette Liquids on Human Mucosal Tissue Cultures of the Oropharynx.
Welz C, Canis M, Schwenk-Zieger S, Becker S, Stucke V, Ihler F, Baumeister P.
J Environ Pathol Toxicol Oncol. 2016;35(4):343-354.

Abstract

The popularity of electronic cigarettes (ECs) is rapidly growing and ECs are claimed to be an uncritically regarded alternative to conventional cigarettes. The mucosal tissue of the upper aerodigestive tract (UADT) is the first contact organ for xenobiotics such as liquids of ECs. The aim of this study is to investigate the bimolecular effects of e-liquids on human pharyngeal tissue cultures to evaluate whether e-liquids and their components present a risk factor for head and neck squamous cell carcinoma. Fresh tissue samples of healthy oropharyngeal mucosa were assembled into mucosal tissue cultures. Two fruit-flavored liquids (FLs), one tobacco-flavored liquid (TL) (all containing nicotine), and the corresponding base mixtures (free of nicotine and flavor) were used in three different dilutions. Cytotoxicity was assessed using the water-soluble tetrazolium-8 assay. DNA fragmentation was quantified using alkaline microgel electrophoresis. All liquids caused a significant reduction in cell viability. FLs especially showed a higher toxicity than TL. DNA fragmentation significantly increased by incubation with FL, whereas treatment with TL did not show serious DNA damage. E-liquids are cytotoxic to oropharyngeal tissue, and some liquids can induce relevant DNA damage. Thus, mutagenicity for mucosa of the UADT and e-liquids as risk factors for head and neck cancer cannot entirely be ruled out. Only the implementation of standards and regulations for liquid production and distribution can ensure a valid scientific investigation and assessment of carcinogenic potential of long-term EC use.

Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping.
Khlystov A, Samburova V.
Environ Sci Technol. 2016 Dec 6;50(23):13080-13085. Epub 2016 Nov 8.

The growing popularity of electronic cigarettes (e-cigarettes) raises concerns about the possibility of adverse health effects to primary users and people exposed to e-cigarette vapors. E-Cigarettes offer a very wide variety of flavors, which is one of the main factors that attract new, especially young, users. How flavoring compounds in e-cigarette liquids affect the chemical composition and toxicity of e-cigarette vapors is practically unknown.

Although e-cigarettes are marketed as safer alternatives to traditional cigarettes, several studies have demonstrated formation of toxic aldehydes in e-cigarette vapors during vaping. So far, aldehyde formation has been attributed to thermal decomposition of the main components of e-cigarette e-liquids (propylene glycol and glycerol), while the role of flavoring compounds has been ignored. In this study, we have measured several toxic aldehydes produced by three popular brands of e-cigarettes with flavored and unflavored e-liquids. We show that, within the tested e-cigarette brands, thermal decomposition of flavoring compounds dominates formation of aldehydes during vaping, producing levels that exceed occupational safety standards. Production of aldehydes was found to be exponentially dependent on concentration of flavoring compounds. These findings stress the need for a further, thorough investigation of the effect of flavoring compounds on the toxicity of e-cigarettes.

Toxicity evaluation of e-juice and its soluble aerosols generated by electronic cigarettes using recombinant bioluminescent bacteria responsive to specific cellular damages.
Bharadwaj S, Mitchell RJ, Qureshi A, Niazi JH.
Biosens Bioelectron. 2017 Apr 15;90:53-60. doi: 10.1016/j.bios.2016.11.026. Epub 2016 Nov 12.

Abstract

Electronic-cigarettes (e-cigarette) are widely used as an alternative to traditional cigarettes but their safety is not well established. Herein, we demonstrate and validate an analytical method to discriminate the deleterious effects of e-cigarette refills (e-juice) and soluble e-juice aerosol (SEA) by employing stress-specific bioluminescent recombinant bacterial cells (RBCs) as whole-cell biosensors. These RBCs carry luxCDABE-operon tightly controlled by promoters that specifically induced to DNA damage (recA), superoxide radicals (sodA), heavy metals (copA) and membrane damage (oprF). The responses of the RBCs following exposure to various concentrations of e-juice/SEA was recorded in real-time that showed dose-dependent stress specific-responses against both the e-juice and vaporized e-juice aerosols produced by the e-cigarette. We also established that high doses of e-juice (4-folds diluted) lead to cell death by repressing the cellular machinery responsible for repairing DNA-damage, superoxide toxicity, ion homeostasis and membrane damage. SEA also caused the cellular damages but the cells showed enhanced bioluminescence expression without significant growth inhibition, indicating that the cells activated their global defense system to repair these damages. DNA fragmentation assay also revealed the disintegration of total cellular DNA at sub-toxic doses of e-juice. Despite their state of matter, the e-juice and its aerosols induce cytotoxicity and alter normal cellular functions, respectively that raises concerns on use of e-cigarettes as alternative to traditional cigarette. The ability of

RBCs in detecting both harmful effects and toxicity mechanisms provided a fundamental understanding of biological response to e-juice and aerosols.

A decade of e-cigarettes: Limited research and unresolved safety concerns.
Kaisar MA, Prasad S, Liles T, Cucullo L.
Toxicology. 2016 Jul 15;365:67-75. doi: 10.1016/j.tox.2016.07.020. Epub 2016 Jul 28.
Review.

Abstract

It is well known that tobacco consumption is a leading cause of preventable deaths worldwide and has been linked to major diseases ranging from cancer to chronic obstructive pulmonary disease, atherosclerosis, stroke and a host of neurological/neurodegenerative disorders. In the past decade a number of alternative vaping products have hit the market, rapidly gaining consumers especially among the younger population. Electronic nicotine delivery systems or e-cigarettes have become the sought-after product due to the belief that they are much safer than traditional cigarettes. However, inadequate research and lack of regulatory guidelines for both the manufacturing process and the content of the vaping solution of the e-cigarette has become a major concern. Highly debated and unresolved questions such as whether e-cigarettes may help smokers quit and whether e-cigarettes will promote the use of nicotine among non-smokers add to the confusion of the safety of e-cigarettes. In this review article, we summarize the current understanding (and lack thereof) of the potential health impacts of e-cigarettes. We will also highlight the most recent studies (in vivo/in vitro) which seem to conflict with the broad safety claims put forward by the manufacturers. Finally, we provide potential solutions to overcome the research gap of the short and long-term health impact of e-cigarettes.

Appendix 2: Recent studies relevant to concerns about nicotine as a cancer promoter.

Grando SA. Connections of nicotine to cancer. Nature Reviews Cancer (2014) 14:419-429 doi:10.1038/nrc3725 http://www.nature.com/nrc/journal/v14/n6/pdf/nrc3725.pdf

This Opinion article discusses emerging evidence of direct contributions of nicotine to cancer onset and growth. The list of cancers reportedly connected to nicotine is expanding and presently includes small-cell and non-small-cell lung carcinomas, as well as head and neck, gastric, pancreatic, gallbladder, liver, colon, breast, cervical, urinary bladder and kidney cancers. The mutagenic and tumour-promoting activities of nicotine may result from its ability to damage the genome, disrupt cellular metabolic processes, and facilitate growth and spreading of transformed cells. The nicotinic acetylcholine receptors (nAChRs), which are activated by nicotine, can activate several signalling pathways that can have tumorigenic effects, and these receptors might be able to be targeted for cancer therapy or prevention. There is also growing evidence that the unique genetic makeup of an individual, such as polymorphisms in genes encoding nAChR subunits, might influence the susceptibility of that individual to the pathobiological effects of nicotine. The emerging knowledge about the carcinogenic mechanisms of nicotine action should be considered during the evaluation of regulations on nicotine product manufacturing, distribution and marketing.

Nordenvall C, Nilsson PJ, Ye W, Andersson TM, Nyrén O. Tobacco use and cancer survival: A cohort study of 40,230 Swedish male construction workers with incident cancer. Int J Cancer 2013; 132 (1):155-61. http://onlinelibrary.wiley.com/doi/10.1002/ijc.27587/epdf (full text)

On theoretical grounds, nicotine has been implicated as a modifier of cancer progression. We investigated possible associations of smoking or use of Scandinavian moist snuff (snus) with survival after cancer among Swedish male construction workers. Snus use is associated with substantial exposure to nicotine but not to the combustion products in smoke. Among 336,381 workers with detailed information on tobacco use in 1971–1992, we observed 40,230 incident cancers. Complete follow-up through 2007 was accomplished through linkage to population and health registers. Hazard ratios (HRs) and 95% confidence intervals (CIs) for death from any cause, cancer-specific death and death from other causes were derived from Cox proportional hazards regression models adjusted for

age at diagnosis, body mass index at study entry and period of diagnosis. Never users of any tobacco served as reference. Increased risks of cancer-specific death were observed both among exclusive smokers ($HR_{all\ cancer}$ 1.15, 95% CI: 1.10–1.21) and never-smoking snus users (1.15, 95% CI: 1.05–1.26). As regards deaths due to other causes, exclusive smokers had higher relative risks than exclusive snus users (p = 0.03). A history of tobacco use, even exclusive use of the seemingly benign snus, is associated with moderately increased cancer-specific mortality. Although nicotine might play a role, the mechanisms warrant further investigation.

Bavara JH, Tae H, Settlage RE, Garner HR. Characterizing the Genetic Basis for Nicotine Induced Cancer Development: A Transcriptome Sequencing Study. PLoS One 2013; Jun 18
DOI: 10.1371/journal.pone.0067252
Nicotine is a known risk factor for cancer development and has been shown to alter gene expression in cells and tissue upon exposure. We used Illumina® Next Generation Sequencing (NGS) technology to gain unbiased biological insight into the transcriptome of normal epithelial cells (MCF-10A) to nicotine exposure. We generated expression data from 54,699 transcripts using triplicates of control and nicotine stressed cells. As a result, we identified 138 differentially expressed transcripts, including 39 uncharacterized genes. Additionally, 173 transcripts that are primarily associated with DNA replication, recombination, and repair showed evidence for alternative splicing. We discovered the greatest nicotine stress response by HPCAL4 (up-regulated by 4.71 fold) and NPAS3 (down-regulated by -2.73 fold); both are genes that have not been previously implicated in nicotine exposure but are linked to cancer. We also discovered significant down-regulation (-2.3 fold) and alternative splicing of NEAT1 (lncRNA) that may have an important, yet undiscovered regulatory role. Gene ontology analysis revealed nicotine exposure influenced genes involved in cellular and metabolic processes. This study reveals previously unknown consequences of nicotine stress on the transcriptome of normal breast epithelial cells and provides insight into the underlying biological influence of nicotine on normal cells, marking the foundation for future studies.
Cardinal A, Nastrucci C, Cesario A, Russo P. Nicotine: specific role in angiogenesis, proliferation and apoptosis. *Critical Reviews in Toxicology*, 2012; 42(1): 68–89
http://www.ncbi.nlm.nih.gov/pubmed/22050423

Nowadays, tobacco smoking is the cause of ~5-6 million deaths per year, counting 31% and 6% of all cancer deaths (affecting 18 different organs) in middle-aged men and women, respectively. Nicotine is the addictive component of tobacco acting on neuronal nicotinic receptors (nAChR). Functional nAChR, are also present on endothelial, haematological and epithelial cells. Although nicotine itself is regularly not referred to as a carcinogen, there is an ongoing debate whether nicotine functions as a 'tumour promoter'. Nicotine, with its specific binding to nAChR, deregulates essential biological processes like regulation of cell

proliferation, apoptosis, migration, invasion, angiogenesis, inflammation and cell-mediated immunity in a wide variety of cells including foetal (regulation of development), embryonic and adult stem cells, adult tissues as well as cancer cells. Nicotine seems involved in fundamental aspects of the biology of malignant diseases, as well as of neurodegeneration. Investigating the biological effects of nicotine may provide new tools for therapeutic interventions and for the understanding of neurodegenerative diseases and tumour biology.

Momi N, Kaur S, Ponnusamy MP, Kumar S, Wittel UA, Batra SK. Interplay between smoking-induced genotoxicity and altered signaling in pancreatic carcinogenesis. Carcinogenesis. 2012 Sep;33(9):1617-28. doi: 10.1093/carcin/bgs186. Epub 2012 May 23.

Despite continuous research efforts directed at early diagnosis and treatment of pancreatic cancer (PC), the status of patients affected by this deadly malignancy remains dismal. Its notoriety with regard to lack of early diagnosis and resistance to the current chemotherapeutics is due to accumulating signaling abnormalities. Hoarding experimental and epidemiological evidences have established a direct correlation between cigarette smoking and PC risk. The cancer initiating/promoting nature of cigarette smoke can be attributed to its various constituents including nicotine, which is the major psychoactive component, and several other toxic constituents, such as nitrosamines, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and polycyclic aromatic hydrocarbons. These predominant smoke-constituents initiate a series of oncogenic events facilitating epigenetic alterations, self-sufficiency in growth signals, evasion of apoptosis, sustained angiogenesis, and metastasis. A better understanding of the molecular mechanisms underpinning these events is crucial for the prevention and therapeutic intervention against PC. This review presents various interconnected signal transduction cascades, the smoking-mediated genotoxicity, and genetic polymorphisms influencing the susceptibility for smoking-mediated PC development by modulating pivotal biological aspects such as cell defense/tumor suppression, inflammation, DNA repair, as well as tobacco-carcinogen metabolization. Additionally, it provides a large perspective toward tumor biology and the therapeutic approaches against PC by targeting one or several steps of smoking-mediated signaling cascades.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3514894/
Petros WP, Younis IR, Ford JN, Weed SA. Effects of tobacco smoking and nicotine on cancer treatment. Pharmacotherapy. 2012 Oct;32(10):920-31. doi: 10.1002/j.1875-9114.2012.01117. http://www.ncbi.nlm.nih.gov/pubmed/23033231
A substantial number of the world's population continues to smoke tobacco, even in the setting of a cancer diagnosis. Studies have shown that patients with cancer who have a history of smoking have a worse prognosis than nonsmokers. Modulation of several physiologic processes involved in drug disposition has been associated with long-term

exposure to tobacco smoke. The most common of these processes can be categorized into the effects of smoking on cytochrome P450-mediated metabolism, glucuronidation, and protein binding. Perturbation in the pharmacokinetics of anticancer drugs could result in clinically significant consequences, as these drugs are among the most toxic, but potentially beneficial, pharmaceuticals prescribed. Unfortunately, the effect of tobacco smoking on drug disposition has been explored for only a few marketed anticancer drugs; thus, little prescribing information is available to guide clinicians on the vast majority of these agents. The carcinogenic properties of several compounds found in tobacco smoke have been well studied; however, relatively little attention has been given to the effects of nicotine itself on cancer growth. Data that identify nicotine's effect on cancer cell apoptosis, tumor angiogenesis, invasion, and metastasis are emerging. The implications of these data are still unclear but may lead to important questions regarding approaches to smoking cessation in patients with cancer.

Catassi A, Servent S, Paleari L, Cesario A, Russo P. Multiple roles of nicotine on cell proliferation and inhibition of apoptosis: implications on lung carcinogenesis. Mutat Res. 2008 Sep-Oct;659(3):221-31. doi: 10.1016/j.mrrev.2008.04.002. Epub 2008 Apr 11.
The genotoxic effects of tobacco carcinogens have long been recognized, the contribution of tobacco components to cancerogenesis by cell surface receptor signaling is relatively unexplored. Nicotine, the principal tobacco alkaloid, acts through nicotinic acetylcholine receptor (nAChR). nAChR are functionally present on human lung airway epithelial cells, on lung carcinoma [SCLC and NSCLC] and on mesothelioma and build a part of an autocrine-proliferative network that facilitates the growth of neoplastic cells. Different nAChR subunit gene expression patterns are expressed between NSCLC from smokers and non-smokers. Although there is no evidence that nicotine itself could induce cancer, different studies established that nicotine promotes in vivo the growth of cancer cells and the proliferation of endothelial cells suggesting that nicotine might contribute to the progression of tumors already initiated. These observations led to the hypothesis that nicotine might be playing a direct role in the promotion and progression of human lung cancers. Here, we briefly overview the role and the effects of nicotine on pulmonary cell growth and physiology and its feasible implications in lung carcinogenesis.

Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicol Teratol. 2008 Jan-Feb;30(1):1-19.
Tobacco use in pregnancy is a leading cause of perinatal morbidity and contributes in major ways to attention deficit hyperactivity disorder, conduct disorders and learning disabilities that emerge in childhood and adolescence. Over the past two decades, animal models of prenatal nicotine exposure have demonstrated that nicotine is a neurobehavioral teratogen that disrupts brain development by preempting the natural, neurotrophic roles

of acetylcholine. Through its actions on nicotinic cholinergic receptors, nicotine elicits abnormalities of neural cell proliferation and differentiation, promotes apoptosis and produces deficits in the number of neural cells and in synaptic function. The effects eventually compromise multiple neurotransmitter systems because of the widespread regulatory role of cholinergic neurotransmission. Importantly, the long-term alterations include effects on reward systems that reinforce the subsequent susceptibility to nicotine addiction in later life. These considerations strongly question the appropriateness of nicotine replacement therapy (NRT) for smoking cessation in pregnant women, especially as the pharmacokinetics of the transdermal patch may actually enhance fetal nicotine exposure. Further, because brain maturation continues into adolescence, the period when smoking typically commences, adolescence is also a vulnerable period in which nicotine can change the trajectory of neurodevelopment. There are also serious questions as to whether NRT is actually effective as an aid to smoking cessation in pregnant women and adolescents. This review considers the ramifications of the basic science findings of nicotine's effects on brain development for NRT in these populations.

Egleton RD, Brown KC, Dasgupta P. Nicotinic acetylcholine receptors in cancer: multiple roles in proliferation and inhibition of apoptosis. Trends Pharmacol Sci. 2008 Mar;29(3):151-8. doi: 10.1016/j.tips.2007.12.006. Epub 2008 Feb 11.
Nicotinic acetylcholine receptors (nAChRs) constitute a heterogeneous family of ion channels that mediate fast synaptic transmission in neurons. They have also been found on non-neuronal cells such as bronchial epithelium and keratinocytes, underscoring the idea that they have functions well beyond neurotransmission. Components of cigarette smoke, including nicotine and NNK [4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone], are agonists of nAChRs. Given the association of tobacco use with several diseases, the non-neuronal nAChR signaling pathway has considerable implications for cancer and cardiovascular disease. Recent studies have shown that alpha7 is the main nAChR subunit that mediates the proliferative effects of nicotine in cancer cells. As a result, alpha7 nAChR might be a valuable molecular target for therapy of cancers such as lung cancer and mesothelioma. Future studies involving the design of nAChR antagonists with improved selectivity might identify novel strategies for the treatment of tobacco-related cancers. Here we review the cellular roles of non-neuronal nAChRs, including regulation of cell proliferation, angiogenesis, apoptosis, migration, invasion and secretion.
Zeilder R, Albermann K, Lang S. Nicotine and apoptosis. Apoptosis. 2007 Nov;12(11):1927-43.
Cigarette smoking is associated with a plethora of different diseases. Nicotine is the addictive component of cigarette but also acts onto cells of the non-neuronal system, including immune effector cells. Although nicotine itself is usually not referred to as a carcinogen, there is ongoing debate whether nicotine functions as a 'tumor enhancer.' By binding to nicotinic acetylcholine receptors, nicotine deregulates essential biological

processes like angiogenesis, apoptosis, and cell-mediated immunity. Apoptosis plays critical roles in a wide variety of physiologic processes during fetal development and in adult tissue and is also a fundamental aspect of the biology of malignant diseases. This review provides an overlook how nicotine influences apoptotic processes and is thus directly involved in the etiology of pathological conditions like cancer and obstructive diseases.

Wickström R. Effects of nicotine during pregnancy: human and experimental evidence. Curr Neuropharmacol. 2007 Sep;5(3):213-22. doi: 10.2174/157015907781695955.
Prenatal exposure to tobacco smoke is a major risk factor for the newborn, increasing morbidity and even mortality in the neonatal period but also beyond. As nicotine addiction is the factor preventing many women from smoking cessation during pregnancy, nicotine replacement therapy (NRT) has been suggested as a better alternative for the fetus. However, the safety of NRT has not been well documented, and animal studies have in fact pointed to nicotine per se as being responsible for a multitude of these detrimental effects. Nicotine interacts with endogenous acetylcholine receptors in the brain and lung, and exposure during development interferes with normal neurotransmitter function, thus evoking neurodevelopmental abnormalities by disrupting the timing of neurotrophic actions. As exposure to pure nicotine is quite uncommon in pregnant women, very little human data exist aside from the vast literature on prenatal exposure to tobacco smoke. The current review discusses recent findings in humans on effects on the newborn of prenatal exposure to pure nicotine and non-smoke tobacco. It also reviews the neuropharmacological properties of nicotine during gestation and findings in animal experiments that offer explanations on a cellular level for the pathogenesis of such prenatal drug exposure. It is concluded that as findings indicate that functional nAChRs are present very early in neuronal development, and that activation at this stage leads to apoptosis and mitotic abnormalities, a total abstinence from all forms of nicotine should be advised to pregnant women for the entirety of gestation.
Full text here http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2656811/

Grozio A, Catassi A, Cavalieri Z, Paleari L, Cesario A, Russo P.
Nicotine, lung and cancer. Anticancer Agents Med Chem. 2007 Jul;7(4):461-6.
The respiratory epithelium expresses the cholinergic system including nicotinic receptors (nAChRs). It was reported that normal human bronchial epithelial cells (BEC), which are the precursor for squamous cell carcinomas, and small airway epithelial cells (SAEC), which are the precursor for adenocarcinomas, have slightly different repertoires of nAChRs. Studies show that nAChRs expressed on lung carcinoma or mesothelioma form a part of an autocrine-proliferative network facilitating the growth of neoplastic cells; others demonstrated that nicotine can promote the growth of colon, gastric, and lung cancers. Nicotine and structurally related carcinogens like NNK [4-(methylnitrosoamino)- 1-(3-

pyridyl)-1-butanone] and NNN (N'-nitrosonornicotine) could induce the proliferation of a variety of small cell lung carcinoma cell lines and endothelial cells and nicotine in non-neuronal tissues -including lung- induces the secretion of growth factors (bFGF, TGF-alpha, VEGF and PDGF), up regulation of the calpain family proteins, COX-2 and VEGFR-2, causing the eventual activation of Raf/MAPK kinase/ERK (Raf/MEK/ERK) pathway contributing to the growth and progression of tumors exposed to nicotine through tobacco smoke or cigarette substitutes. It has been demonstrated that nicotine promotes the growth of solid tumors in vivo, suggesting that might induce the progression of tumors already initiated. While tobacco carcinogens can initiate and promote tumorigenesis, the exposure to nicotine could confer a proliferative advantage to early tumors but there is no evidence that nicotine itself provokes cancer. This is supported by the findings that nicotine can prevent apoptosis induced by various agents - such as chemotherapeutic in NSCLC, conferring a survival advantage as well.

Wu WK, Cho CH. The pharmacological actions of nicotine on the gastrointestinal tract. J Pharmacol Sci. 2004 Apr;94(4):348-58.
Increasing use of tobacco and its related health problems are a great concern in the world. Recent epidemiological findings have demonstrated the positive association between cigarette smoking and several gastrointestinal (GI) diseases, including peptic ulcer and cancers. Interestingly, smoking also modifies the disease course of ulcerative colitis (UC). Nicotine, a major component of cigarette smoke, seems to mediate some of the actions of cigarette smoking on the pathogenesis of GI disorders. Nicotine worsens the detrimental effects of aggressive factors and attenuates the protective actions of defensive factors in the processes of development and repair of gastric ulceration. Nicotine also takes part in the initiation and promotion of carcinogenesis in the GI tract. In this regard, nicotine and its metabolites are found to be mutagenic and have the ability to modulate cell proliferation, apoptosis, and angiogenesis during tumoriogenesis through specific receptors and signalling pathways. However, to elucidate this complex pathogenic mechanism, further study at the molecular level is warranted. In contrast, findings of clinical trials give promising results on the use of nicotine as an adjuvant therapy for UC. The beneficial effect of nicotine on UC seems to be mediated through multiple mechanisms. More clinical studies are needed to establish the therapeutic value of nicotine in this disease.

Zhu B-Q, Heeschen C. Sievers RE, Karliner JS, Parmley WW, Glantz SA, Cooke JP.
Second hand smoke stimulates tumor angiogenesis and growth. Cancer Cell 2003; Sept 191-196.

http://ac.els-cdn.com/S1535610803002198/1-s2.0-S1535610803002198-main.pdf?_tid=ad1f8084-a439-11e5-b823-00000aab0f6c&acdnat=1450300512_9ba5bb948ad346910e374692a9b5715a (full text)

Exposure to second hand smoke (SHS) is believed to cause lung cancer. Pathological angiogenesis is a requisite for tumor growth. Lewis lung cancer cells were injected subcutaneously into mice, which were then exposed to sidestream smoke (SHS) or clean room air and administered vehicle, cerivastatin, or mecamylamine. SHS significantly increased tumor size, weight, capillary density, VEGF and MCP-1 levels, and circulating endothelial progenitor cells (EPC). Cerivastatin (an inhibitor of HMG-coA reductase) or mecamylamine (an inhibitor of nicotinic acetylcholine receptors) suppressed the effect of SHS to increase tumor size and capillary density. Cerivastatin reduced MCP-1 levels, whereas mecamylamine reduced VEGF levels and EPC. These studies reveal that SHS promotes tumor angiogenesis and growth. These effects of SHS are associated with increases in plasma VEGF and MCP-1 levels, and EPC, mediated in part by isoprenylation and nicotinic acetylcholine receptors.

And also:

England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the Developing Human: A Neglected Element in the Electronic Cigarette Debate A 2015 Aug;49(2):286-93. doi: 10.1016/j.amepre.2015.01.015.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594223/pdf/nihms724908.pdf

The elimination of cigarettes and other combusted tobacco products in the U.S. would prevent tens of millions of tobacco-related deaths. It has been suggested that the introduction of less harmful nicotine delivery devices, such as electronic cigarettes or other electronic nicotine delivery systems, will accelerate progress toward ending combustible cigarette use. However, careful consideration of the potential adverse health effects from nicotine itself is often absent from public health debates. Human and animal data support that nicotine exposure during periods of developmental vulnerability (fetal through adolescent stages) has multiple adverse health consequences, including impaired fetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents. Measures to protect the health of pregnant women and children are needed and could include (1) strong prohibitions on marketing that increase youth uptake; (2) youth access laws similar to those in effect for other tobacco products; (3) appropriate health warnings for vulnerable populations; (4) packaging to prevent accidental poisonings; (5) protection of non-users from exposure to secondhand electronic cigarette aerosol; (6) pricing that helps minimize youth initiation and use; (7) regulations to reduce product addiction potential and appeal for youth; and (8) the age of legal sale.

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