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

Page last updated: 11 January 2018

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

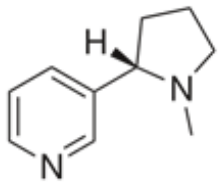
Substance summary

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

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

References

1 World Health Organisation, "Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS)" WHO Framework Convention on Tobacco Control, Geneva, 2016.

2 World Health Organisation, "Electronic Nicotine Delivery Systems" WHO Framework Convention on Tobacco Control, Geneva, 2014.

3 M. L. Goniewicz , J. Knysak , M. Gawron, L. Kosmider, A. Sobczak and J. Kurek, "Levels of Selected Carcinogens and Roxicants in Vapour from Electronic Cigarettes" *Tobacco Control,* vol. 23, no. 2, pp. 133-139, 2014.

4 S. S. Hecht, S. G. Carmella, D. Kotandeniya, M. E. Pillsbury, M. Chen, B. W. Ransom, R. Isaksson Vogel, E. Thompson, S. E. Murphy and D. K. Hatsukami, "Evaluation of Toxicant and Carcinogen Metabolites in the Urine of e-Cigarette Users Versus Cigarette Smokers" *Nicotine & Tobacco Research,* pp. 1-6, 2014.

5 N. Lindson-Hawley, J. Hartmann-Boyce, T. R. Fanshawe, R. Begh, A. Farley and T. Lancaster, "Interventions to Reduce Harm from Continued Tobacco Use" *Cochrane Database of Systematic Reviews,* no. 10, 2016.

6 D. J. Nutt, L. D. Phillips, D. Balfour, H. V. Curran, M. Dockrell, J. Foulds, K. Fagerstrom, K. Letlape, A. Milton, R. Polosa, J. Ramsey and D. Sweanor, "Estimating the Harms of Nicotine-Containing Products Using the MCDA Approach" *European Addiction Research,* vol. 20, no. 5, pp. 218-225, 2014.

7 The Lancet, "Public Health England's Evidence-Based Confusion" *The Lancet,* vol. 386, p. 829, 2015.

8 M. Mckee and S. Capewell, "Evidence about Electronic Cigarettes: Foundation Built on Rock or Sand?" *BMJ,* vol. 351, 2015.

9 T. Cheng, "Chemical Evaluation of Electronic Cigarettes" *Tobacco Control,* vol. 23, no. Suppl 2, pp. ii11-7, 2014.

10 O. Geiss, I. Bianchi and J. Barrero-Moreno, "Correlation of Volatile Carbonyl Yields Emitted by E-cigarettes with the Temperature of the Heating Coil and the Perceived Sensorial Quality of the Generated Vapours" *International Journal of Hygiene and Environmental Health,* vol. 219, no. 3, pp. 268-277, 2016.

11 C. Hutzler, M. Paschke, S. Kruschinski, F. Henkler, J. Hahn and A. Luch, "Chemical Hazards Present in Liquids and Vapors of Electronic Cigarettes" *Archives of Toxicology,* vol. 88, pp. 1295-1308, 2014.

12 R. P. Jensen, W. Luo, J. F. Pankow, R. M. Strongin and D. H. Peyton, "Hidden Formaldehyde in E-cigarette Aerosols" *The New England Journal of Medicine,* vol. 372, no. 4, pp. 392-394, 2015.

13 M. Sleiman, J. M. Logue, V. N. Montesinos, M. L. Russell, M. I. Litter, L. A. Gundel and H. Destaillats, "Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals" *Environmental Science & Technology,* vol. 50, no. 17, pp. 9644-9651, 2016.

14 L. Kosmider, A. Sobczak, M. Fik, J. Knysak, M. Zaciera, J. Kurek and M. L. Goniewicz, "Carbonyl Compounds in Electronic Cigarette Vapors – Effects of Nicotine Solvent and Battery Output Voltage" *Nicotine & Tobacco Research,* vol. 16, no. 10, pp. 1319-1326, 2014.

15 W. Visser, L. Geraets, W. Klerx, L. Hernandez, E. Stephens, E. Croes, P. Schwillens, H. Cremers, P. Bos and R. Talhout, "The Health Risks of Using E-cigarettes" National Institute for Public Health and the Environment, Bilthoven, 2015.

16 A. El-Hellani, R. Salman, R. El-Hage, S. Talih, N. Malek, R. Baalbaki, N. Karaoghlanian, R. Nakkash, A. Shihadeh and N. A. Saliba, "Nicotine and Carbonyl Emissions From Popular Electronic Cigarette Products: Correlation to Liquid Composition and Design Characteristics" *Nicotine & Tobacco Research,* vol. Oct, 2016.

17 A. Khlystov and V. Samburova, "Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping" *Environmental Science & Technology,* vol. 50, no. 23, pp. 13080-13085, 2016.

18 International Agency for Research on Cancer (IARC), "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 100F (29)" WHO, 2012.

19 S. Uchiyama, K. Ohta, Y. Inaba and N. Kunungita, "Determination of Carbonyl Compounds Generated from the E-cigarette using Coupled Silica Cartridges Impregnated with Hydroquinone and 2,4-Dinitrophenylhydrazine, Followed by High-Performance Liquid Chromatography" *Analytical Sciences,* vol. 29, pp. 1219-1222, 2013.

20 K. Kreiss, A. Gomaa, G. Kullman, K. Fedan, E. Simoes and P. Enright, "Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant" *New England Journal of Medicine,* vol. 347, no. 5, pp. 330-338, 2002.

21 P. Harber, K. Saechao and C. Boomus, "Diacetyl-Induced Lung Disease" *Toxicological Reviews,* vol. 25, no. 4, pp. 261-272, 2006.

22 R. Behar, B. Davis, Y. Wang, V. Bahl, S. Lin and P. Talbot, "Identification of Toxicants in Cinnamon-Flavored Electronic Cigarette Refill Liquids" *Toxicology in Vitro,* vol. 28, no. 2, pp. 198-208, 2014.

23 L. Kosmider, A. Sobczak, A. Prokopowicz, J. Kurek, M. Zaciera, J. Knysak, D. Smith and M. L. Goniewicz, "Cherry-flavoured Electronic Cigarettes Expose Users to the Inhalation Irritant, Benzaldehyde" *Thorax,* vol. 71, no. 4, pp. 376-377, 2016.

24 R. M. Pellegrino, B. Tinghino, G. Mangiaracina, A. Marani, M. Vitali, C. Protano, J. F. Osborn and M. S. Cattaruzza, "Electronic Cigarettes: an Evaluation of Exposure to Chemicals and Fine Particulate Matter (PM)" *Annali di Igiene,* vol. 24, no. 4, pp. 279-288, 2012.

25 W. Schober, K. Szendrei, W. Matzen, H. Osiander-Fuchs, D. Heitmann, T. Schettgen, R. A. Jorres and H. Fromme, "Use of Electronic Cigarettes (E-cigarettes) Impairs Indoor Air Quality and Increases FeNO Levels of E-cigarette Consumers" *International Journal of Hygiene and Environmental Health,* vol. 217, pp. 628-637, 2014.

26 T. Schripp, D. Markewitz, E. Uhde and T. Salthammer, "Does E-cigarette Consumption Cause Passive Vaping?" *Indoor Air,* vol. 23, pp. 25-31, 2013.

27 J. Zhao, G. Pyrgiotakis and P. Demokritou, "Development and Characterization of Electronic-Cigarette Exposure Generation System (Ecig-EGS) for the Physico-Chemical and Toxicological Assessment of Electronic Cigarette Emissions" *Inhalation Toxicology,* vol. 28, no. 14, pp. 658-669, 2016.

28 Environmental Protection Agency, "Integrated Science Assessment for Particulate Matter (Final Report)" U.S. Environmental Protection Agency, Washington DC, 2009.

29 World Health Organisation, "WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide: Summary of Risk Assessment" WHO, Geneva, 2006.

30 M. Williams, A. Villarreal, K. Bozhilov, S. Lin and P. Talbot, "Metal and Silicate Particles Including Nanoparticles are Present in Electronic Cigarette Cartomizer Fluid and Aerosol" *PLoS One,* vol. 8, no. 3, p. e57987, 2013.

31 V. B. Mikheev, M. C. Brinkman, C. A. Granville, S. M. Gordon and P. I. Clark, "Real-Time Measurement of Electronic Cigarette Aerosol Size Distribution and Metals Content Analysis" *Nicotine & Tobacco Research,* vol. May, 2016.

32 C. A. Hess, P. Olmedo, A. Navas-Acien, W. Goessler, J. E. Cohen and A. M. Rule, "E-cigarettes as a Source of Toxic and Potentially Carcinogenic Metals" *Environmental Research,* vol. 152, pp. 221-225, 2017.

33 J. Hartmann-Boyce, H. McRobbie, C. Bullen, R. Begh, L. F. Stead and P. Hajek, "Electronic Cigarettes for Smoking Cessation (Review)" *Cochrane Database of Systematic Reviews,* no. 9, 2016.

34 M. R. Gualano, S. Passi, F. Bert, G. La Torre, G. Scaioli and R. Siliquini, "Electronic Cigarettes: Assessing the Efficacy and the Adverse Effects through a Systematic Review of Published Studies" *Journal of Public Health,* vol. 37, no. 3, pp. 488-497, 2015.

35 S. F. Rudy and E. L. Durmowicz, "Electronic Nicotine Delivery Systems: Overheating, Fires and Explosions" *Tobacco Control,* vol. Mar, 2016.

36 K. Chatham-Stephens, R. Law, E. Taylor, S. Kieszak, P. Melstrom, R. Bunnell, B. Wang, H. Day, B. Apelberg, L. Cantrell, H. Foster and J. G. Schier, "Exposure Calls to U. S. Poison Centers Involving Electronic Cigarettes and Conventional Cigarettes-September 2010-December 2014" *Journal of Medical Toxicology,* 2016.

37 F. Davanzo, L. Settimi, G. Milanesi, F. Giordano, F. M. Sesana, A. Celentano, E. Urbani, G. Panzavolta, L. Cossa, A. Tomoiaga, A. Travaglia and V. Dimasi, "Surveillance of Hazardous Exposures to Electronic Cigarettes in Italy" *Clinical Toxicology,* vol. 52, no. Supp, pp. 336-337, 2014.

38 A. Kamboj, H. A. Spiller, M. J. Casavant, T. Chounthirath and G. A. Smith, "Pediatric Exposure to E-Cigarettes, Nicotine, and Tobacco Products in the United States" *Pediatrics,* vol. 137, no. 6, 2016.

39 S. W. Lindberg, N. Ebbehoej, J. Bang and L. B. Christensen, "Nicotine Poisoning Related to the Use of E-cigarettes" *Clinical Toxicology,* vol. 53, no. 4, 2015.

40 S. Pajarre-Sorsa, M. Saukkonen and K. Hoppu, "Calls Concerning Electronic Cigarettes to the Finnish Poison Information Centre" *Clinical Toxicology,* vol. 52, no. Supp, p. 337, 2014.

41 E. Thomas, R. A. Spears, G. Alldridge, C. V. Krishna, J. P. Thompson, M. Eddleston, J. A. Vale and S. H. L. Thomas, "E-cigarette Liquid Refills – a Safe Beverage? Analysis of Enquiries to the UK National Poisons Information Service from 2007 to 2013" *Clinical Toxicology,* vol. 52, no. Supp, pp. 338-339, 2014.

42 J. P. Vakkalanka, L. S. Hardison and C. P. Holstege, "Epidemiological Trends in Electronic Cigarette Exposures Reported to U.S. Poison Centers" *Clinical Toxicology,* vol. 52, no. 5, pp. 542-548, 2014.

43 I. M. R. Hess, K. Lachireddy and A. Capon, "A Systematic Review of the Health Risks from Passive Exposure to Electronic Cigarette Vapour" *Public Health Research and Practice,* vol. 26, no. 2, 2016.

44 E. L. Durmowicz, S. F. Rudy and I. L. Chen, "Electronic Cigarettes: Analysis of FDA Adverse Experience Reports in Non users" *Tobacco Control,* vol. 25, no. 2, p. 242, 2016.

45 S. Lee, R. Grana and S. Glantz, "Eletronic Cigarette Use Among Korean Adolescents: A Cross-Sectional Study of Market Penetration, Dual Use, and Relationship to Quit Attempts and Former Smoking" *J Adolesc Health,* vol. 54, pp. 684-690, 2014.

46 B. Eastwood, M. J. Dockrell, D. Arnott, J. Britton, H. Cheeseman, M. J. Jarvis and A. McNeill, "Electronic Cigarette Use in Young People in Great Britain 2013-2014" *Public Health,* vol. 129, no. 9, pp. 1150-1156, 2015.

47 T. Singh, R. A. Arrazola, C. G. Corey, C. G. Husten, L. J. Neff, D. M. Homa and B. A. King, "Tobacco Use Among Middle and High School Students — United States, 2011-2015" *Morbidity and Mortality Weekly Report,* vol. 65, no. 14, 2016.

48 J. White, J. Li, R. Newcombe and D. Walton, "Tripling Use of Electronic Cigarettes Among New Zealand Adolescents Between 2012 and 2014" *The Journal of Adolescent Health,* vol. 56, no. 5, pp. 522-528, 2015.

49 J. M. Kinnunen, H. Ollila, P. L. Lindfors and A. H. Rimpelä, "Changes in Electronic Cigarette Use from 2013 to 2015 and Reasons for Use Among Finnish Adolescents" *International Journal of Environmental Research and Public Health,* vol. 13, no. 11, 2016.

50 K. Chatterjee, B. Alzghoul, A. Innabi and N. Meena, "Is Vaping a Gateway to Smoking: a Review of the Longitudinal Studies" *Int J Adolesc Med Health,* 2016.

51 J. L. Barrington-Trimis, R. Urman, K. Berhane, J. B. Unger, T. B. Cruz, M. A. Pentz, J. M. Samet, A. M. Leventhal and R. McConnell, "E-Cigarettes and Future Cigarette Use" *Pediatrics,* vol. 138, no. 1, 2016.

52 J. B. Unger, D. W. Soto and A. Leventhal, "E-cigarette Use and Subsequent Cigarette and Marijuana Use Among Hispanic Young Adults" *Drug and Alcohol Dependence,* 2016.

53 T. R. Spindle, M. M. Hiler, M. E. Cooke and T. Eissenberg, "Electronic Cigarette Use and Uptake of Cigarette Smoking: A Longitudinal Examination of U.S. College Students" *Addictive Behaviors,* vol. 67, pp. 66-72, 2017.

54 T. A. Wills, J. D. Sargent, F. X. Gibbons, I. Pagano and R. Schweitzer, "E-cigarette Use is Differentially Related to Smoking Onset Among Lower Risk Adolescents" *Tobacco Control,* 2016.

55 J. Huh and A. M. Leventhal, "Progression of Poly-Tobacco Product Use Patterns in Adolescents" *American Journal of Preventive Medicine,* vol. 51, no. 4, pp. 513-517, 2016.

56 A. M. Leventhal, D. R. Strong, M. G. Kirkpatrick, J. B. Unger, S. Sussman, N. R. Riggs, M. D. Stone, R. Khoddam, J. M. Samet and J. Audrain-McGovern, "Association of Electronic Cigarette Use with Initiation of Combustible Tobacco Product Smoking in Early Adolescence" *JAMA,* vol. 314, no. 7, pp. 700-707, 2015.

57 J. Hahn, Y. B. Monakhova, J. Hengen, M. Kohl-Himmelseher, J. Schassler, H. Hahn, T. Kuballa and D. W. Lachenmeier, "Electronic Cigarettes: Overview of Chemical Composition and Exposure Estimation" *Tobacco Induced Diseases,* vol. 12, no. 1, p. 23, 2014.

58 S. Han, H. Chen, X. Zhang, T. Liu and Y. Fu, "Levels of Selected Groups of Compounds in Refill Solutions for Electronic Cigarettes" *Nicotine & Tobacco Research,* vol. 18, no. 5, pp. 708-714, 2016.

59 M. E. Hadwiger, M. L. Trehy, W. Ye, T. Moore, J. Allgire and B. Westenberger, "Identification of Amino-tadalafil and Rimonabant in Electronic Cigarette Products Using High Pressure Liquid Chromatography with Diode Array and Tandem Mass Spectrometric Detection" *Journal of Chromatography,* vol. 1217, no. 48, pp. 7547-7555, 2010.

60 J. G. Allen, S. S. Flanigan, M. LeBlanc, J. Vallarino, P. MacNaughton, J. H. Stewart and D. C. Christiani, "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes" *Environmental Health Perspectives,* 2015.

61 Australian Competition and Consumer Commission, "ACCC Takes Action Against E-cigarette Suppliers for Alleged Misleading "No Toxic Chemicals" Claims" 20 June 2016. Online. Available: https://www.accc.gov.au/media-release/accc-takes-action-against-e-cigarette-suppliers-for-alleged-misleading-%E2%80%9Cno-toxic-chemicals%E2%80%9D-claims. Accessed 25 November 2016.

62 K. Buettner-Schmidt, D. R. Miller and N. Balasubramanian, "Electronic Cigarette Refill Liquids: Child-Resistant Packaging, Nicotine Content, and Sales to Minors" *Journal of Pediatric Nursing,* vol. 31, no. 4, pp. 373-379, 2016.

63 B. Davis, M. Dang, J. Kim and P. Talbot, "Nicotine Concentrations in Electronic Cigarette Refill and Do-it-yourself Fluids" *Nicotine & Tobacco Research,* vol. 17, no. 2, pp. 134-141, 2015.

64 M. Williams, A. Villareal, B. Davis and P. Talbot, "Comparison of the Performance of Cartomizer Style Electronic Cigarettes from Major Tobacco and Independent Manufacturers" *PLoS One,* vol. 11, no. 2, 2016.

65 M. Famele, J. Palmisani, C. Ferranti, C. Abenavoli, L. Palleschi, R. Mancinelli, R. M. Fidente, G. de Gennaro and R. Draisci, "Liquid Chromatography with Tandem Mass Spectrometry Method for the Determination of Nicotine and Minor Tobacco Alkaloids in Electronic Cigarette Refill Liquids and Second-hand Generated Aerosol" *Journal of Separation Science,* vol. Dec, 2016.

66 M. L. Goniewicz, P. Hajek and H. McRobbie, "Nicotine Content of Electronic Cigarettes, its Release in Vapour and its Consistency Across Batches: Regulatory Implications" *Addiction,* vol. 109, no. 3, pp. 500-507, 2014.

67 U.S. Food and Drug Administration, "Evaluation of E-cigarettes" U.S. Food and Drug Administration, St Louis, MO, 2009.

68 J. Regueiro, A. Giri and T. Wenzl, "Optimization of a Differential Ion Mobility Spectrometry-Tandem Mass Spectrometry Method for High-Throughput Analysis of Nicotine and Related Compounds: Application to Electronic Cigarette Refill Liquids" *Analytical Chemistry,* vol. 88, no. 12, pp. 6500-6508, 2016.

69 C. Pisinger and M. Døssing, "A Systematic Review of Health Effects of Electronic Cigarettes" *Preventive Medicine,* vol. 69, pp. 248-260, 2014.