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Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure

Final report prepared for the National Health and Medical Research Council

November 2021

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DECLARATIONS OF INTEREST

The authors of this report have no affiliations with or involvement in any organisations or entities with any financial or non-financial interest in e-cigarettes. One of the authors (MM) has previously worked in Tobacco Control in New Zealand and another (EB) has published research on the health effects of smoking; all authors have authored papers based on the e-cigarettes program of work.

NOTE

This Supplementary Report should be read in conjunction with the main report – *Electronic cigarettes and health outcomes: systematic review of evidence*.

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Abbreviations

ANU	Australian National University
COPD	Chronic obstructive pulmonary disease
CSIRO	Commonwealth Scientific and Industrial Research Organisation
ENDS	Electronic Nicotine Delivery System
ENNDS	Electronic Non-nicotine Delivery System
EVALI	Electronic cigarette, or Vaping, Associated Lung Injury
NASEM	US National Academies of Sciences, Engineering and Medicine
NHMRC	National Health and Medical Research Council of Australia
NRT	Nicotine Replacement Therapy
PHE	Public Health England
SCHEER	European Union Scientific Committee on Health, Environmental and Emerging Risks
SIDS	Sudden Infant Death Syndrome
THC	Tetrahydrocannabinol
USPSTF	US Preventive Services Task Force

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Executive Summary

Supplementary Report Two

November 2021

Emily Banks, Amelia Yazidjoglou, Katie Beckwith, Sinan Brown, Melonie Martin

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine.

This document provides supplementary material to the *Electronic cigarettes and health outcomes: systematic review of evidence*. It also provides additional discussion on aspects of the risks and benefits of e-cigarette use in smokers and factors influencing the balance of safety and efficacy of e-cigarettes as an aid to smoking cessation.

Aim and Methods

This report responds to the request for additional evidence and analyses from the Australian National Health and Medical Research Council's Electronic Cigarette Working Committee by supplementing the material presented in the *Electronic cigarettes and health outcomes: systematic review of evidence*, using the studies identified in the *Review* as well as additional evidence as applicable, to support the development of the NHMRC CEO Statement on electronic cigarettes. The report comprises:

1. A review of the evidence on the effects of e-cigarette use on the developing foetal and adolescent brain.
2. Discussion that gives consideration to the risks and benefits of e-cigarette use on smokers.
3. Reference to the report on nicotine dose and concentration and factors relating to the safety of e-cigarettes and their efficacy for smoking cessation.

For detailed methods, see the *Electronic cigarettes and health outcomes: systematic review of evidence*. Where applicable, methods were an extension of those from the main reviews. Where additional methods were adopted, they are outlined in the relevant section.

Key Summary Points

Review – Foetal and adolescent brain development

- There is no available direct evidence on the effects of e-cigarette use on foetal and adolescent brain development.
- Maternal smoking during pregnancy and consequent exposure to nicotine has been linked to sudden infant death syndrome, cognitive, attentional and auditory processing deficits, disruptive behaviours and smoking initiation in offspring.
- Smoking during adolescence has a range of impacts on brain development that have largely been attributed to nicotine, including long term smoking/nicotine addiction, impairments in memory, anxiety disorders, depression, abuse of substances other than tobacco and disruptive disorders.

Risk and benefits of long term e-cigarette use on smokers - Discussion

- While some of the risks of e-cigarette use will accrue to the smokers themselves, others – such as poisoning, environmental impacts, use by non-smokers and increased smoking uptake in non-smokers – will also affect other family and community members.
- Most smokers who use e-cigarettes continue to smoke and the commonest pattern of e-cigarette use currently is dual ongoing tobacco smoking and e-cigarette use.
- Multiple risks of nicotine e-cigarettes have been identified and their short and long-term effects on important clinical outcomes are unknown. Hence, the balance of safety and efficacy of the use of e-cigarettes in smokers is not known.
- Given the extreme harms of smoking, the balance of probabilities may be that e-cigarettes are beneficial in some smokers who use them to quit promptly and completely, bearing in mind the current inability to determine the overall balance of harms and benefits in smokers.

Summary of report on factors influencing the balance of safety and efficacy of e-cigarettes as an aid to smoking cessation

- Nicotine e-cigarettes for smoking cessation:
 - There is limited evidence that freebase nicotine e-cigarettes used in the clinical context are efficacious as an aid for smoking cessation compared to no intervention/usual care and to approved NRT.
 - The balance of risks and benefits of e-cigarettes for smoking cessation is unclear.
- Nicotine dose and concentration:
 - The dose of nicotine received by an e-cigarette user is highly variable and is influenced by the device, nicotine concentration, user behaviour and other factors

- Evidence on risks relating to e-cigarettes
 - There is an overall paucity of evidence regarding the health effects of e-cigarettes.
 - Identified risks with moderate to strong evidence include poisoning, injuries, nicotine toxicity from inhalation – including seizures, addiction, e-cigarette or vaping associated lung injury (EVALI), increased uptake of combustible tobacco smoking, and indoor air pollution, environmental waste and fires.
 - There is currently insufficient evidence to characterise the risks of other important clinical outcomes in relation to e-cigarettes, including those relating to cancer, cardiovascular disease, respiratory disease (other than EVALI), reproductive and pregnancy outcomes, mental health problems and neurological diseases (apart from seizures).
- Factors increasing e-cigarette related risks
 - Current evidence indicates a range of factors are likely to increase the risks relating to nicotine e-cigarettes include: greater nicotine concentrations; greater e-liquid volumes; at home dilution; flavourings apart from tobacco; packaging that is not child resistant; inadequate or inaccurate product labelling; and factors that increase the likelihood of nicotine e-cigarette use in the broader community, including among youth and non-smokers, such as: availability; advertising and promotion; low cost; lack of enforcement of legislation; public and private sector influence of the nicotine industry; misinformation about health impacts; and high concentration nicotine salt products. Risks may also be greater in certain priority populations including Aboriginal and Torres Strait Islander communities and people with mental health problems.
- Measures likely to reduce e-cigarette-related risks. For example:
 - Implementing general measures to avoid e-cigarette use in non-smokers and youth, and use which is not for the purpose of smoking cessation, including but not limited to: appropriate enforcement of policies and regulations; avoiding widespread use including through availability as consumer products; bans on advertising/promotion; banning flavours other than tobacco, increasing costs; bans on use in smokefree public spaces; avoiding high concentration nicotine salt products; appropriate monitoring of e-cigarette use and tobacco smoking; supporting e-cigarette users to quit; banning non-nicotine e-cigarettes and availability of appropriate information on risks.

Purpose and scope

This document provides supplementary material to the *Electronic cigarettes and health outcomes: systematic review of evidence*, commissioned by the Australian Department of Health. The National Health and Medical Research Council of Australia (NHMRC) commissioned the current supplementary report to inform the update of the NHMRC CEO Statement on electronic cigarettes (e-cigarettes). The document includes:

- A review of the effects of e-cigarette use on the developing foetal and adolescent brain.
- Discussion that gives consideration to the risks and benefits of long-term e-cigarette use on smokers.
- A summary of and reference to the report on nicotine dose and concentration and factors relating to the safety of e-cigarettes and their efficacy for smoking cessation.

The work was undertaken independently by researchers from the National Centre for Epidemiology and Population Health, Research School of Population Health, the Australian National University.

Background

E-cigarettes are a diverse group of battery-powered devices that create an aerosol from a liquid (e-liquid). Although the composition of e-liquid varies, it typically contains a range of chemicals including propylene glycol – mainly used in e-cigarettes as a solvent to produce visible aerosol – glycerine and flavouring agents, and commonly contains nicotine.

The *Electronic cigarettes and health outcomes: systematic review of evidence* considered the current evidence regarding the direct effects of e-cigarettes on health. This included a summary of evidence from peer-reviewed and grey literature and evidence from other major international reviews including the National Academies of Sciences, Engineering and Medicine (NASEM),¹ Public Health England,² Commonwealth Scientific and Industrial Research Organisation (CSIRO),³ Irish Health Research Board,⁴ US Preventive Services Task Force (USPSTF)⁵ and European Union Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)⁶ reviews. See the *Electronic cigarettes and health outcomes: systematic review of evidence* for more detail on the background.

Aims

This report aims to supplement the material presented in the *Electronic cigarettes and health outcomes: systematic review of evidence*. It uses studies identified in the *Review* as well as additional evidence as applicable, to support the development of the NHMRC CEO Statement on electronic cigarettes.

The report is comprised of three main parts:

1. A review of the effects of e-cigarette use on the developing foetal and adolescent brain.
2. Discussion that gives consideration to the risks and benefits of long-term e-cigarette use on smokers.

3. Reference to the report on nicotine dose and concentration and factors relating to the safety of e-cigarettes and their efficacy for smoking cessation.

Methods

For detailed methods, see the main report - *Electronic cigarettes and health outcomes: systematic review of evidence*. Where additional methods were adopted, they are outlined in the relevant section.

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Foetal and Adolescent Brain Development

Background

The *Electronic cigarettes and health outcomes: systematic review of evidence* considered the current evidence regarding the direct effects of e-cigarettes on health. The main review considered all evidence on reproductive and developmental outcomes while this report exclusively considers developing foetal, child and adolescent brain outcomes.

The foetus undergoes rapid and extensive development while in utero. During this critical phase of human development, a foetus is vulnerable to compounds that cross the maternal placental barrier, such as nicotine.¹ Nicotine, via exposure from passive or active smoker mothers, crosses both the placental barrier and the blood brain barrier and can be found at concentrations 15% higher than in mothers depending on dose and time of exposure.⁷ Another critical period of brain development occurs during adolescence during which the brain undergoes major reorganisation of neurochemical systems and structure and leads to a window of vulnerability.^{8,9} Exposure to nicotine at these critical developmental stages has the potential to impact both short- and long-term health outcomes.

Aims

This section presents findings from the *Electronic cigarettes and health outcomes: systematic review of evidence* specifically related to the effects of e-cigarettes on the developing foetal, child and adolescent brain. Developmental and reproductive evidence not related to the brain is not mentioned here and is considered in the larger report. A summary of the evidence from other reviews has also been provided.

Methods

The full methods have been detailed in the *Electronic cigarettes and health outcomes: systematic review of evidence*. Findings from major independent international reports on e-cigarettes and health were reviewed. A top-up review was conducted to update the evidence since the 2018 review of the US National Academies of Science, Engineering and Medicine (NASEM). Original peer-reviewed articles reporting on the relationship of e-cigarette exposure to foetal and adolescent brain development published after the NASEM review were included in the top-up review. Only studies in humans and with either smoker or non-smoker comparators were included. Full inclusion and exclusion criteria can be found in Appendix 3 in the *Electronic cigarettes and health outcomes: systematic review of evidence*. The systematic review protocol was published on PROSPERO (CRD42020200673). Findings from the top-up review, the NASEM review and other major international reviews were combined in evidence synthesis.

Additional discussion of the impacts of smoking and nicotine on the developing brain from major international reviews including the NASEM,¹ Public Health England,² Commonwealth Scientific and Industrial Research Organisation (CSIRO),³ Irish Health Research Board,⁴ US Preventative Services Task Force,⁵ Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)⁶ and US Surgeon General¹⁰ reviews, has also been summarised and presented.

Findings

Evidence from the Electronic cigarettes and health outcomes: systematic review of evidence

Out of the 6,558 articles screened, no studies on the effects of e-cigarette exposure on brain development in foetuses, children and adolescents were identified. The review identified three studies on reproductive and developmental outcomes not related to the brain and three studies on neurological outcomes not related to development.

Summary of the evidence from major international reviews

No articles that directly assessed the impact of e-cigarettes on foetal or adolescent brain development were identified in the NASEM review.¹ In lieu of any studies on e-cigarette exposure, nicotine exposure from combustible cigarettes and approved nicotine replacement therapies was considered. The NASEM review reported that prenatal exposure to compounds of combustible cigarettes elevates the of risk of developing behavioural difficulties (such as attention deficit hyperactivity disorder) in children of mothers who smoked combustible cigarettes during pregnancy. Combustible cigarette exposure has also been linked to an increased risk of sudden infant death syndrome (SIDS) although the role of nicotine in SIDS remained unclear. It should be noted that although nicotine may be a causative agent in outcomes related to exposure to combustible cigarettes, many other compounds are involved and determining the specific causative agents is problematic. The authors conclude that there is *“insufficient evidence whether or not maternal e-cigarette use affects fetal development”*.¹

The SCHEER review⁶ identified one study that investigated the effect of e-cigarettes and nicotine replacement therapies on foetal brain development, however, the review by Sailer et al. was not able to locate any studies assessing e-cigarette use during pregnancy.¹¹ The SCHEER review also identified one review examining clinical and preclinical data regarding adolescent brain sensitivity to nicotine.⁶ Yuan et al. found that nicotine exposure in adolescents can induce modifications in neural signalling which may have implications for teen addiction, cognition and regulation of emotions.⁸

The US Surgeon General review provided the most comprehensive discussion of nicotine on foetal and adolescent brain development. As no evidence on e-cigarettes was available, smoking was used to examine the effects of nicotine on the adolescent brain finding an age-dependent susceptibility to nicotine as a

neurobiological insult.¹⁰ Adolescent smoking can evoke long term changes in the neural reward systems that increases the risk of comorbid substance abuse (for example, combustible cigarettes and other nicotine products, alcohol and other drugs) and reward-seeking behaviour and decreases aversion behaviours.¹⁰ Compared to non-smokers, adolescent smokers report more attentional problems and decreased prefrontal cortex activation.^{12,13} Furthermore, the severity of chronic impairments in working memory accuracy increases with earlier smoking initiation age.¹⁴ Tobacco use and dependence in adolescents also increases the risk of anxiety disorders with disorder onset positively associated with earlier ages of initiation.^{15,16} There is evidence of a bidirectional relationship between adolescent smoking and disruptive disorders such as attention deficit hyperactivity disorder and oppositional defiant disorder and depression.^{17,18}

Adolescence is a life stage when many risk-related behaviours are defined and commence.¹⁹ A significant concern of nicotine exposure during this life stage is the implications for long term nicotine and tobacco dependence. Evidence from both human studies and animal models indicate an age-dependent susceptibility to nicotine, with greater susceptibility from exposure at younger ages.¹⁰ Patterns of addiction to tobacco smoking, primarily driven by addiction to nicotine, demonstrate that smokers almost always commence during childhood, when aged less than 18, and smoking and addiction then persist into adult life.²⁰ This is supported by animal data: in adolescent rats, nicotine enhances neuronal activity in several reward-related brain regions leading to the strengthening of the behavioural reward responses to nicotinic stimuli.^{21,22} This effect occurs more robustly in adolescent than adult rats and persists even at low doses.^{23,24} The US Surgeon General concludes that *“given the existing evidence from human and animal studies of the detrimental impact of nicotine exposure on adolescent brain development, the use of e-cigarettes by youth should be avoided and actively discouraged”*.¹⁰

Similar to adolescent brain development, there were no studies on - the effects of maternal e-cigarette exposure on foetal development, instead, evidence from mothers who smoked was considered in the US Surgeon General’s review.¹⁰ Maternal smoking has been causally associated with SIDS with 20-29% of infant deaths attributed to smoking during pregnancy in 2002.²⁵ Nicotine is known to impede foetal arousal and although the aetiology of SIDS is unclear, evidence suggests impaired foetal arousal may be an underlying cause.²⁶ Modifications in the structure of the foetal corpus callosum (a major structure connecting the two sides of the brain) and resultant cognitive deficits has also been linked to prenatal exposure to smoking.²⁷⁻²⁹ Maternal smoking during pregnancy has been associated with deficits in auditory processing in infants and children.³⁰ Implications of auditory process deficits extend beyond hearing functionality as language development and speech development rely on auditory stimuli. Maternal smoking has been identified as a risk factor for initiation, regular use, and dependence on combustible cigarettes in adolescent offspring attributed to disruptions in neural and dopamine systems that heightened sensitivity to nicotine.^{31,32} Disruptive behaviours - such as attention deficit hyperactivity disorder, conduct disorder and oppositional defiant

disorder - among infants and children have been causally association with mothers who smoke during pregnancy. The US Surgeon General concludes that *“pregnant women and women intending to become pregnant should be cautioned against using e-cigarettes to avoid unnecessary nicotine exposure to their baby”*.¹⁰

The Public Health England evidence update (2020) specifically examined e-cigarette use during pregnancy. No studies on foetal brain development were identified and the authors concluded that there was a “lack of evidence... on the effects of vaping on maternal health or pregnancy outcomes”.² No papers or discussion of the impact of e-cigarettes or nicotine on foetal and adolescent brain development were included in the CSIRO,³ Irish Health Research Board⁴ and US Preventative Services Task Force³³ reviews.

Summary

- There is no available direct evidence on the effects of e-cigarette use on foetal and adolescent brain development.
- Maternal smoking during pregnancy and consequent exposure to nicotine has been linked to SIDS, cognitive, attentional and auditory processing deficits, disruptive behaviours and smoking initiation in offspring.
- Smoking during adolescence has a range of impacts on brain development that have largely been attributed to nicotine, including long term smoking/nicotine addiction, impairments in memory, anxiety disorders, depression, abuse of substances other than tobacco and disruptive disorders.

Risk and benefits of long-term e-cigarette use on smokers - Discussion

Background

In many countries e-cigarettes are implicitly or explicitly marketed as aids to smoking cessation and less harmful alternatives to conventional cigarettes. The NHMRC has requested a discussion that gives consideration to the risks and benefits of long-term e-cigarette use on smokers.

Aims and Methods

This section reproduces the discussion from the draft *Electronic cigarettes and health outcomes: systematic review of evidence* related to the effects of e-cigarettes on the health of smokers. The methods are detailed in that review, and include identification and synthesis of the worldwide evidence from major published reports and relevant studies published since the NASEM report. Throughout the report, where possible, evidence on e-cigarette effects specific to current, past and never-smokers was identified.

Findings

Table 1. Summary of evidence on the effects of e-cigarettes on health outcomes

Health outcome group	Summary conclusions from evidence review
Dependence and abuse liability	<ul style="list-style-type: none">• Among non-smokers, there is substantial evidence that e-cigarette use results in dependence on e-cigarettes• Among smokers there is limited evidence that e-cigarette use results in dependence on e-cigarettes. There is limited evidence that e-cigarettes have lower abuse liability than combustible cigarettes and limited evidence that e-cigarettes have a higher abuse liability than nicotine replacements therapy products among smokers.• Among smokers, there is insufficient evidence whether abuse liability risk is influenced by flavour and nicotine concentration variations.
Cardiovascular health outcomes	<ul style="list-style-type: none">• There is no available evidence on the effect of e-cigarette use on the risk of clinical cardiovascular disease outcomes, such as myocardial infarction, stroke or cardiovascular mortality.• There is no available evidence on e-cigarette use and the risk of subclinical atherosclerosis-related outcomes such as carotid intima-media thickness and coronary artery calcification.• Among non-smokers, there is insufficient evidence that e-cigarette use is related to other cardiovascular outcomes, including: increased blood pressure, heart rate, autonomic control and arterial stiffness; reduced endothelial function, hand microcirculation and cardiac function/geometry; and cardiac device interference.• Among smokers, there is: moderate evidence that use of e-cigarettes increases heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use; and limited evidence that use increases endothelial dysfunction, and that long term use after switching from combustible cigarette smoking decreases blood pressure.
Cancer	<ul style="list-style-type: none">• There is no available evidence on the relationship of e-cigarette use to invasive cancer risk.• There is no available evidence on the relationship of e-cigarette use to the risk of precancer/subclinical cancer outcomes.

Health outcome group	Summary conclusions from evidence review
Respiratory disease	<ul style="list-style-type: none"> • There is conclusive evidence that the use of e-cigarettes can cause lung injury (EVALI) among smokers and non-smokers. Current evidence is that this lung injury is largely related to e-cigarettes delivering THC and/vitamin E acetate, and 14% of cases were in patients reporting the use of nicotine-delivering products only, indicating that these products can cause EVALI. • There is insufficient evidence on the relationship of e-cigarette use to other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers and no available evidence in non-smokers. • There is insufficient evidence for a reduction in respiratory exacerbations and disease progression among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use e-cigarettes. • There is limited evidence in non-smokers and insufficient evidence in smokers that e-cigarette use decreases spirometry parameters up to 25 minutes post exposure. • There is insufficient evidence in smokers and non-smokers that e-cigarette use affects spirometry parameters 30 minutes to two hours after exposure. • There is limited evidence that e-cigarette use increases respiratory resistance and impedance in healthy and asthmatic smokers up to 30 minutes post exposure. • There is insufficient evidence on the effect of e-cigarettes on exhaled breath outcomes among non-smokers and smokers (healthy and asthmatic). • There is insufficient evidence on the relationship of e-cigarette use to other respiratory measures (sinonasal symptoms, airway hyperresponsiveness) in smokers and no available evidence in non-smokers.
Oral health	<ul style="list-style-type: none"> • There is no available evidence on the relationship of e-cigarette use to clinical or intermediate/subclinical oral health outcomes in exclusive e-cigarette users, independent of the effect of smoking. • There is insufficient evidence of reduced plaque, gingival and papillary bleeding in smokers switching to e-cigarette use. • In populations including exclusive e-cigarette users, dual users, and non-smokers (never and former smokers), there is insufficient evidence as to the relationship of e-cigarette use to increased gum disease, bone loss around the teeth and any periodontal disease.
Developmental and reproductive effects	<ul style="list-style-type: none"> • There is no available evidence on the effect of e-cigarette use on development in children or adolescents. • There is insufficient evidence as to the effect of e-cigarette use on adverse foetal and pregnancy outcomes, such as low birth weight, preterm birth, Apgar score and small-for-gestational-age, among exclusive e-cigarette users and dual users. • There is no available evidence as to how use of e-cigarettes affects other reproductive outcomes.
Burns and injuries	<ul style="list-style-type: none"> • There is conclusive evidence that e-cigarettes can cause burns and injuries, which can be severe and can result in death.
Poisonings	<ul style="list-style-type: none"> • There is conclusive evidence that intentional or accidental exposure to nicotine e-liquids can lead to poisoning, which can be severe and can result in death. A significant number of accidental poisonings occur in children under the age of six. • There is conclusive evidence that use of e-cigarettes can result in nicotine toxicity.
Mental health effects	<ul style="list-style-type: none"> • There is no available evidence as to how e-cigarettes use affects clinical mental health outcomes. • There is insufficient evidence as to the relationship of e-cigarette use to depressive symptoms and no available evidence regarding their effects on other mental health measures.

Health outcome group	Summary conclusions from evidence review
Environmental hazards with health implications Error! Reference source not found.	<ul style="list-style-type: none"> • There is conclusive evidence that e-cigarette use results in increased airborne particulate matter in indoor environments. • There is limited evidence that e-cigarette use results in increased concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces. • There is insufficient evidence that e-cigarette use results in increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls. • There is substantial evidence that e-cigarettes can cause fires and environmental waste and insufficient evidence as to the extent that these present a hazard to human health.
Neurological outcomes	<ul style="list-style-type: none"> • There is conclusive evidence that the use of e-cigarettes can cause seizures. • There is limited evidence that injuries due to e-cigarette explosions can lead to nerve damage. • There is no available evidence as to how use of e-cigarettes affects the risk of other clinical neurological outcomes.
Sleep	<ul style="list-style-type: none"> • There is no available evidence as to the effect of use of e-cigarettes on clinical sleep outcomes.
Adverse Events (less serious)	<ul style="list-style-type: none"> • There is moderate evidence that less serious adverse events – such as throat irritation, cough, dizziness, headache and nausea – occur with use of nicotine e-cigarettes.
Optical health	<ul style="list-style-type: none"> • There is no available evidence on the relation of e-cigarette use to clinical optical outcomes. • There is insufficient evidence on the relation of e-cigarette use to corneal epithelial thickness or pre-corneal tear film stability and no evidence on other optical outcomes.
Wound healing	<ul style="list-style-type: none"> • There is no available evidence as to the effect of e-cigarette use on clinical or subclinical wound healing outcomes
Olfactory outcomes	<ul style="list-style-type: none"> • There is no available evidence on the effect of use of e-cigarettes on clinical olfactory outcomes. • There is insufficient evidence on the relationship between use of e-cigarettes and olfactory measures.
Endocrine outcomes	<ul style="list-style-type: none"> • There is no available evidence on the effect of use of e-cigarettes on clinical and subclinical endocrine outcomes.
Allergic diseases	<ul style="list-style-type: none"> • There is no available evidence on the relationship of e-cigarette use to allergic diseases.
Haematological outcomes	<ul style="list-style-type: none"> • There is no available evidence on the relationship of e-cigarette use to haematological outcomes.
Smoking uptake	<ul style="list-style-type: none"> • There is strong evidence that never smokers who use e-cigarettes are on average around three times as likely than those who do not use e-cigarettes to initiate cigarette smoking. • There is strong evidence that non-smokers who use e-cigarettes are also around three times as likely as those who do not use e-cigarettes to become current cigarette smokers. • There is limited evidence that former smokers who use e-cigarettes are more likely to relapse and resume current smoking than former smokers who have not used e-cigarettes.
Smoking cessation	<ul style="list-style-type: none"> • There is limited evidence that, in the clinical context, freebase nicotine e-cigarettes may be more efficacious for smoking cessation than existing NRT, and that nicotine e-cigarettes may be more efficacious than no intervention or usual care. • Trials demonstrating efficacy were limited to products with freebase nicotine concentrations $\leq 20\text{mg/mL}$. There is no evidence that nicotine salt products are efficacious for smoking cessation. • There is insufficient evidence that freebase nicotine e-cigarettes are efficacious for smoking cessation, compared to non-nicotine e-cigarettes or that non-nicotine e-cigarettes are efficacious for smoking cessation compared to counselling or approved NRT. • There is insufficient evidence that freebase nicotine e-cigarettes are efficacious outside the clinical setting. • No evidence on nicotine salt products was located and their efficacy for smoking cessation is unknown. • There is limited evidence that use of nicotine e-cigarettes for smoking cessation results in greater ongoing exposure to nicotine than approved NRT, through ongoing exclusive e-cigarette use or dual use if smoking continues.

Discussion relevant to smokers (reproduced from *Electronic cigarettes and health outcomes: systematic review*)

Evidence on the balance of risks and benefits of an exposure is fundamental to determining appropriate regulatory measures, including use in consumer or therapeutic settings. The balance of risks and benefits of e-cigarettes, and regulatory options, will be explored more fully in our forthcoming *Public Health Assessment of Electronic Cigarettes*; they are considered briefly below.

Tobacco smoking is exceptionally harmful to health and quitting brings commensurate benefits. The goal of smoking cessation is complete abstinence. Even so-called “light smoking” - including smoking fewer than 10 cigarettes a day - carries large health risks. This includes a doubling in cardiovascular mortality and over nine-fold risks of lung cancer compared to never smoking.^{34,35} The commonest pattern of use of e-cigarettes is dual use in combination with smoking. Such use appears to help smokers to offset important tobacco control measures – for example, by being cheaper and more socially acceptable than smoking, by permitting use where smoking is banned and by being perceived as less harmful to health. Reducing the number of cigarettes smoked is also a common reason given for e-cigarette use among smokers. If dual use results in prolongation of smoking, the net impact may well be harmful, even if the number of cigarettes smoked per day is reduced, as noted by the WHO:

“...modest prolongation of duration of use may overwhelm the effect of a substantial reduction in intensity of exposure in determining the risk for individual smokers. Therefore, a product with lower levels of toxic emissions (e.g., smokeless product) which enabled a person to continue his or her use of a more toxic product (e.g., cigarette) may result in increased harm if cessation of the more toxic product is delayed.”³⁶

While many of the risks related to e-cigarettes apply broadly to those using them, the population, comparator and nature of use will influence the absolute balance of harms and benefit relating to e-cigarettes. Furthermore, exposure to nicotine from e-cigarettes is highly variable, according to device and e-liquid characteristics, as well as user behaviour and characteristics. The risks identified in this summary of worldwide evidence apply to the general population – regardless of smoking status – apart from increased risk of combustible smoking uptake in non-smoking e-cigarette users and dual use in smokers. There is also virtually complete uncertainty about a range of important outcomes.

Among non-smokers, there is strong evidence that use of e-cigarettes is harmful to health overall in that multiple health harms and no health benefits were identified in this population. Given the evidence regarding the direct health risks of e-cigarette use, the evidence that they generate new tobacco smokers – with established high levels of harm – the uncertainty about major health outcomes, and the importance of low

smoking uptake as a driver of progress against tobacco, use of e-cigarettes in non-smokers, especially youth, represents a serious public health risk.

These risks are reinforced by the fact that use by children and adolescents is increasing rapidly in many parts of the world.^{37,38} Youth is the time when risk behaviours – including long term tobacco use – are established, as well as a time of rapid brain development and vulnerability. Current global patterns of e-cigarette use cause and are the consequence of large-scale nicotine addiction in young people – a negative outcome in itself – with contextual evidence for this review indicating likely effects on future addiction and brain functioning, including impacts on anxiety, concentration and memory (see section 3.5). In 2018, the US Surgeon General declared the large-scale use of e-cigarettes among youth to be an “epidemic”³⁹ and the Secretary of the US Department of Health and Human Services, noted recently “The United States has never seen an epidemic of substance use arise as quickly as our current epidemic of youth use of e-cigarettes”.⁴⁰

In common with non-smokers, health impacts in ex-smokers will be reduced if use is avoided, compared to ex-smokers who do not use e-cigarettes. The risk of relapse and resumption of smoking is increased in ex-smokers who use e-cigarettes, compared to ex-smokers who do not use them.⁴¹

Smokers are vulnerable to the adverse health consequences of e-cigarette identified here. While some of the risks of e-cigarette use will accrue these individuals, others – such as poisoning, environmental impacts, use by non-smokers and increased smoking uptake in non-smokers – will also affect other community members. Those affected can also include family members of smokers using e-cigarettes – as was seen with the poisoning death of Baby J in Australia in 2018.⁴² Since multiple risks of nicotine e-cigarettes have been identified here and their long-term effects are unknown, the balance of safety and efficacy of the use of e-cigarettes in smokers is unclear.

The US Preventive Services Task Force concluded in its most recent review in 2021 that “The evidence on the use of e-cigarettes for tobacco smoking cessation in adults, including pregnant persons, is insufficient, and the balance of benefits and harms cannot be determined.”^{5,33} This conclusion is consistent with the current status of e-cigarettes in the US, EU, Australia and elsewhere in that they are not registered therapeutic goods and, as such, their quality, safety and efficacy with respect to smoking cessation has not been established. Given the extreme harms of smoking, the balance of probabilities may be that e-cigarettes are beneficial in some smokers who use them and cease smoking entirely, bearing in mind the current inability to determine the overall balance of harms and benefits in smokers. As noted above, the most common pattern of e-cigarette use in many countries, including Australia, is dual tobacco smoking and e-cigarette use which may increase risks. The most recent review from the World Health Organization states:

“Although the consequences for long-term effects on morbidity and mortality have not yet been studied sufficiently, ENDS and ENNDS are not safe for young people, pregnant women and adults

who have never smoked. While it is expected that use of ENDS and ENNDS in these groups might increase their health risks, non-pregnant adult smokers who completely and promptly switch from combustible tobacco cigarettes to use of unadulterated and appropriately regulated ENDS and ENNDS alone might reduce their health risks.”⁴³

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Summary of report on nicotine dose and concentration and factors relating to the safety of e-cigarettes and their efficacy for smoking cessation

This summary is reproduced from Banks E, Buckley N, Day C, Martin M. Nicotine dose and nicotine e-liquid concentration and other factors relating to electronic cigarette safety and efficacy as an aid to smoking cessation in Australia: rapid review. Report for the Australian Department of Health, August 2021.

Please refer to the full document for details.

Background

Electronic cigarettes (e-cigarettes) are often marketed as aids to smoking cessation and smoking cessation is a commonly reported reason for use. No e-cigarette products have been approved by the Australian Therapeutic Goods Administration as smoking cessation aids; the situation is similar in many other countries.

A scheduling decision announced by the Australian Therapeutic Goods Administration in December 2020 clarified that consumers will require a valid Australian medical prescription to access nicotine e-cigarettes (also known as electronic nicotine delivery systems, ENDS) and certain other nicotine products from 1 October 2021. In June 2021, the Therapeutic Goods Administration introduced TGO standard 110, which includes: a limit on nicotine concentration in e-liquids in Australia of 100mg/mL; no restriction on use of flavours, aside from those found to carry specific health risks; no limit on the volume of e-liquid that can be prescribed; ingredient, nicotine and warning statement labelling and child resistant packaging for products supplied in Australia: and, for supply via the Personal Importation Scheme, up to 3 months' supply can be imported, with no more than 15 months' supply in a 12-month period – ingredient list, nicotine concentration and warning statement labelling and child resistant packaging are not required.

Aim and Methods

This report aims to support informed decision-making on e-cigarettes by bringing together current relevant evidence on nicotine dose and e-liquid concentration and other considerations in relation to the safety and efficacy of e-cigarettes from: the Australian National University (ANU) completed review on e-cigarettes and smoking behaviour; the completed ANU review on the efficacy of e-cigarettes as an aid to smoking cessation; preliminary evidence from the ANU draft review of e-cigarettes and health outcomes, incorporating findings from major international reports; and a rapid evidence scan of published and grey literature.

Key Summary Points

Context

- Nicotine is one of the most addictive substances known.
- The potentially lethal dose of nicotine is 5mg/kg.
- There is wide variation in the regulation of e-cigarettes internationally; Australia's prescription-only model is unique.
- Overall, 35 of the 36 countries that regulate the concentration of nicotine in e-liquids – including EU countries, the UK and Canada – stipulate an upper limit of 20mg/mL.
- EU regulations limit e-cigarette refill containers sizes to 10 mL and device tank sizes to 2 mL.

Nicotine e-cigarettes for smoking cessation

- There is limited evidence that e-cigarettes are efficacious as an aid for smoking cessation compared to no intervention/usual care and to approved nicotine replacement therapy (NRT).
- The balance of risks and benefits of e-cigarettes for smoking cessation is unclear.
- The Royal Australian College of General Practitioners currently recommends use of e-cigarettes for smoking cessation only in smokers who have tried other pharmacotherapies unsuccessfully, who have been informed about the risks and uncertainties.
- The two trials which found significantly greater efficacy of nicotine e-cigarettes compared to NRT were conducted within UK smoking cessation services and were limited to concentrations $\leq 20\text{mg/mL}$ – effectively 18mg/mL or lower. The trial with available data reported use of median nicotine concentrations of 10mg/mL at commencement and 6mg/mL at 6 month follow up.

Nicotine dose and concentration

- The dose of nicotine received by an e-cigarette user is highly variable and is influenced by the device, nicotine concentration, user behaviour and other factors.
- Nicotine e-cigarette use has been shown to reduce cravings and nicotine withdrawal symptoms.
- Commercial information generally recommends nicotine e-liquid concentration for vape pens and less powerful devices for smoking cessation of 3- $<12\text{mg/mL}$ for light to moderate smokers and 12-18mg/mL for heavy smokers. Lower concentrations are recommended for more powerful devices, which have heating coils of higher wattage, which allow greater aerosolisation of e-liquid.⁶
- Average delivered doses of nicotine comparable to or in excess of conventional cigarettes are observed with use of e-cigarettes, including for products in the $<20\text{mg/mL}$ dose range.

Evidence on risks relating to electronic cigarettes

- In the context of the overall paucity of evidence regarding the health effects of e-cigarettes, the identified risks of e-cigarettes with moderate to strong evidence are:

- Poisoning – accidental and intentional
- Injuries due to burns and explosions
- Nicotine toxicity from inhalation, including seizures
- Addiction
- E-cigarette or vaping use-associated lung injury (EVALI)
- Increased uptake of combustible tobacco smoking among non-smoking e-cigarette users
- Increased indoor air pollution, environmental waste and fires.
- There is currently insufficient or no available evidence to characterise the risks of other clinical disease outcomes in relation to e-cigarette use, including those relating to cancer, cardiovascular disease, respiratory disease (other than EVALI), reproductive and pregnancy outcomes, mental health problems and neurological diseases (apart from seizures).

Factors increasing e-cigarette related risks

- Current evidence indicates that the following factors are likely to increase the risks relating to nicotine e-cigarettes:
- Greater nicotine concentrations.
- “At home” dilution and other preparation of e-liquids.
- Availability of large volumes of e-liquid.
- Highly variable nicotine delivery according to device, device modification.
- Flavourings and products likely to appeal to children, adolescents and non-smokers, including high concentration “pods” utilising nicotine salts.
- Inadequate or inaccurate labelling.
- Packaging which is not child resistant.
- Multiple prescriptions and dispensings of e-cigarette products (“doctor shopping”).
- Long term use.
- Addition of THC, vitamin E acetate and other adulteration.
- Anything that increases the likelihood of nicotine e-cigarette use in the broader community, including among youth and non-smokers. This includes but is not limited to: availability; diversion; use in smoke-free public spaces; availability of non-nicotine e-cigarettes; advertising/promotion; low cost; lack of enforcement of legislation; public and private sector influence of the nicotine industry; misinformation about health impacts; and high concentration nicotine salt products.
- Risks may also be greater in certain priority populations including Aboriginal and Torres Strait Islander communities and people with mental health problems.

Measures likely to reduce e-cigarette-related risks

Strategies likely to reduce risks relating to e-cigarettes in the Australian context include:

- Maximising population-level tobacco control strategies.
- Banning the sale of non-nicotine e-cigarettes.
- Using approved, registered smoking cessation products where possible.
- Restricting e-liquids and pods to nicotine concentrations of 20mg/mL or less.
- Limiting volumes of e-liquid able to be imported. As noted above, EU regulations limit e-liquid refill containers to 10 mL in total.
- Avoiding “at home” dilution and other preparation. Pre-mixed “ready to vape” e-liquids and “closed” systems are options here, in addition to restricting liquid nicotine concentrations to those that can be used without dilution (i.e. 20mg/mL or less).
- Avoiding flavourings likely to appeal to children, adolescents and non-smokers.
- Avoiding devices and products known to appeal to and increase use in children and adolescents, including high concentration nicotine pods.
- Identifying devices delivering consistent doses of nicotine for given concentration.
- Ensuring high quality labelling and child resistant packaging. Since these are not required under products acquired through the Personal Importation Scheme, risks related to these will be reduced if patients avoid this and receive them through Australian suppliers.
- Implementing multiple measures to avoid e-cigarette use in non-smokers and youth, and use in smokers which is not for the purpose of smoking cessation, including but not limited to: appropriate enforcement of policies and regulations; avoiding widespread use including through availability as consumer products; bans on advertising/promotion; increasing costs; bans on use in smokefree public spaces; avoiding high concentration nicotine salt products; appropriate monitoring of e-cigarette use and tobacco smoking; supporting e-cigarette users to quit; banning non-nicotine e-cigarettes and availability of appropriate information on risks.

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