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The Royal Australasian College of Physicians' submission to the Therapeutic Goods Administration

Interim Decision on Nicotine Scheduling
November 2020

About The Royal Australasian College of Physicians (RACP)

The RACP trains, educates and advocates on behalf of 18,000 physicians and 8,500 trainee physicians, across Australia and Aotearoa/New Zealand. The RACP represents a broad range of medical specialities including general medicine, paediatrics and child health, cardiology, respiratory medicine, infectious diseases, neurology, oncology, public health medicine, occupational and environmental medicine, sexual health medicine, rehabilitation medicine, geriatric medicine, addiction medicine and palliative medicine.

Executive Summary

The Therapeutic Goods Administration (TGA) is seeking feedback on an interim decision to amend the current Poisons Standard regarding nicotine.

The Poisons Standard classifies medicines and poisons into Schedules grouped by similar regulatory control over them. The various schedules set the level of control on the availability of poisons to the public (higher number, higher control). This scheduling is not solely based on toxicity but takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance. It does not indicate that the poison is available; nor that is has been approved or is efficacious for any use that may be specified in a Schedule; nor does it negate any obligation for registration of a therapeutic good, or agricultural or veterinary chemical product containing that poison.

The proposed amendments with a recommended implementation date of 1 June 2021 are to:

- Reschedule nicotine for human use from Schedule 7 (which refers to a "Dangerous Poison") to Schedule 4 (which refers to a "Prescription Only Medicine"),
- Delete Schedule 6 (which refers to a "Poison"), as there are no longer products containing nicotine for the treatment of animals which Schedule 6 relates to,
- Make changes to Appendix D (which refers to additional controls on possession or supply of poisons included in Schedule 4 or 8) to ensure that possession of Schedule 4 products containing nicotine must be in accordance with a legal prescription.
- Seek feedback on the requirements for child resistant closures for liquid nicotine products.

These changes do not apply to nicotine used for smoking, or for existing smoking cessation aids (which are both currently exempt from scheduling), therefore it applies to nicotine used for e-cigarettes, e-juice, heat-not-burn tobacco products, chewing tobacco, snuff and other novel nicotine products.

There is support from the Cancer Council Australia, Pharmacy Guild, Public Health Association of Australia, Royal Australian and New Zealand College of Psychiatrists and the Australian Medical Association, received in response to the pre-meeting consultation.

The RACP Position

The RACP supports the *intent* of the TGAs interim decision to amend the current Poisons Standard to further clarify the regulation of nicotine, however the RACP has concerns and issues which must be addressed before implementation:

- The potential medico-legal, ethical and professional responsibilities for the medical profession in taking on the prescribing role for a product unapproved by the TGA as a therapeutic product for smoking cessation and containing a poison, taking essentially a 'gatekeeper role' in lieu of regulation.
- Full consideration of the feasibility and quality of any prescribing guidelines when the current evidence base is insufficient to inform which nicotine e-cigarettes to recommend as well as the doses, frequency and prescription duration, given the vast range of e-cigarette products on the market, with unknown quality and safety standards and no conclusive evidence of effectiveness to aid quitting. Any guideline must align with the principles of evidence-based practice or QUM framework.
- The inclusion of a specific counselling point on not prescribing to people under 18, the risks of sharing prescribed medication and cessation of e-cigarette use during pregnancy in the prescribing guidelines.
- Allow for capturing more of the growing evidence base and the results from the NHMRC review currently underway.

Rationale for caution

- **In our view, not smoking tobacco or using e-cigarettes remain the safest options for the community. For those seeking to quit smoking, the RACP advocates for the TGA approved smoking cessation products. In the face of contradictory evidence on many aspects of e-cigarettes, the principles of the precautionary approach and upholding public health and safety should be applied and take precedence.**
- The 2020 government commissioned Australian National University preliminary report did not find nicotine e-cigarettes to be more effective than no intervention, non-nicotine e-cigarettes, or nicotine replacement therapy in aiding smoking cessation. It found that nicotine e-cigarettes contribute to prolonged nicotine use[1]. In Australia, the 2019 National Drug Strategy Household Survey (NDSHS) has found that roughly two-thirds of current smokers and 1 in 5 non-smokers aged 18–24 reported having tried e-cigarettes[2]. A wide range of advertising and marketing strategies have been used to particularly target the youth market, including production innovation and celebrity endorsement[3].
- There are currently still a wide range of existing risks and benefits for which there is not strong evidence including the use of e-cigarettes as a smoking cessation tool, the adverse health impacts of vaping, renormalising smoking, the 'gateway effect, nicotine dependence and safety and quality.
- The risks of prescribing a wide range of commercial products outside usual standards of required scientific evidence of safety and effectiveness, which doctors have no high-quality knowledge to base any such prescribing decisions.

Recommendations

The RACP supports the *intent* of the proposed amendment to the nicotine scheduling with the caveat that the risks attached with the mechanism of prescribing unapproved nicotine e-cigarette products and the issue of the lack of high-quality evidence to inform prescribing guideline development be dealt with (which are the core concerns of the RACP) before implementation.

To protect youth, never smokers and former smokers, access to nicotine e-cigarettes must be confined to smokers who are unable to quit smoking as the treatment option of last resort. Non-nicotine containing e-cigarettes must be included in and subject to state tobacco control legislation to tighten their sale and promotion. Without proper planning and consultation, the regulatory changes being proposed may not be implemented as intended but invite further problems. We also ask the TGA to strengthen the public health protection aspect of any potential regulatory change by considering the following recommendations:

- E-cigarette products should be manufactured to suitable quality and safety standards.
- E-cigarette product packaging and labelling requirements should be implemented, including disclosure of all ingredients and their concentrations in e-liquid, child-resistant packaging, plain packaging rules and health warning labels.
- The sale and supply of e-cigarettes (with or without nicotine) to minors, including access through personal importation scheme, must be prohibited and stringently enforced in all Australian states and territories. E-cigarettes must not be allowed to be promoted in a way that encourages youth uptake or smoking initiation.
- The use of e-cigarettes should be banned in all areas that are designated to be smoke-free by Australia's state and territory laws.

[1] Australian National University. Summary report on use of e-cigarettes and relation to tobacco smoking uptake, smoking cessation, relevant to Australian context. Available from: https://openresearch-repository.anu.edu.au/bitstream/1885/211618/3/E-cigarettes%20smoking%20behaviour%20summary%20report%20final%20200924.pdf
[2] National Drug Strategy Household Survey 2019. Chapter 2:Tobacco Smoking Available at: https://www.aihw.gov.au/getmedia/3564474e-f7ad-461c-b918-7f8de03d1294/aihw-phe-270-NDSHS-2019.pdf.aspx?inline=true
[3] US Department of Health and Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General. Chapter 4: Activities of the E-Cigarette Companies. https://www.ncbi.nlm.nih.gov/books/NBK538679/

RACP's comments on the interim decision to amend the nicotine entry in the Poisons Standard

The RACP welcomes the opportunity to provide comments to the TGA's consultation on the interim decision of the Secretary's delegate in relation to nicotine.

Whilst in support of the intent by the TGA to clarify the classification of nicotine containing e-cigarettes, the RACP would recommend that further time is provided before implementation is considered to address the concerns and issues that have been raised in relation to the prescribing of non-TGA approved e-cigarette products and for the development of prescribing guidelines.

Nicotine is highly addictive

Nicotine is highly addictive and a poison[4]. The RACP considers that the current evidence base for e-cigarettes is still insufficient to ascertain its long-term impacts and health risks at the individual and the population levels. We advise that not smoking tobacco or using e-cigarettes remain the safest options for the community. TGA approved smoking cessation pharmacotherapies and technologies accompanied with behavioural counselling should be the first-line treatment for smoking cessation and must be widely available and accessible by smokers who wish to quit.

Given the rising uptake of e-cigarettes among teens in countries where the sale of e-cigarettes is legal, the RACP is particularly concerned about youth vaping and progression to cigarette smoking and stresses that its access must be confined to smokers who are unable to quit smoking as the treatment option of last resort. Our concern is validated by the National Academies of Sciences, Engineering and Medicine (NASEM)'s 2018 report "Public Health Consequences of E-Cigarettes"[5] and a recent Australian summary report[6] on use of e-cigarettes and the relationship to tobacco smoking uptake and smoking cessation. We urge the Secretary's delegate to examine the detailed findings of this report as it is the first government commissioned report into e-cigarettes relevant to the Australian context.

We note the ACCS-ACMS's risk and benefit assessment of the matter in accordance with section 52E (1) of the Therapeutic Goods Act 1989. Our comments and evidence to support delegate's decision are outlined in the assessment format below, in line with the 2018 RACP policy on e-cigarettes. Areas of further consideration in relation to this interim decision are included at the end of this submission.

1. Comments on Child Resistant Closures for Liquid Nicotine Products

As pointed out by the Delegate, the risk of accidental exposure or ingestion of nicotine in e-liquid is a growing problem. The RACP recognises that since e-cigarettes became available on the market, the number of calls to poisons control centres relating to unintentional exposure to nicotine in e-liquids among young children has increased considerably in Australia and other countries[7] [8] [9]. These incidents primarily involved ingestion of the e-liquid, inhalation of the aerosol as well as eye and skin irritation.

[4] World Health Organization. Gender, women, and the tobacco epidemic 2010 [137-49]. Available at: http://www.who.int/tobacco/publications/gender/en_tfi_gender_women_addiction_nicotine.pdf
[5] National Academies of Sciences E, and Medicine; Health and Medicine, Public Health Consequences of E-Cigarettes. 2018
[6] Banks E, Beckwith K, Joshy G. Summary report on use of e-cigarettes and impact on tobacco smoking uptake and cessation, relevant to the Australian context. Commissioned Report for the Australian Government Department of Health, September 2020. Available at: http://hdl.handle.net/1885/211618.
[7] Wylie C, Heffernan A, Brown JA, Cairns R, Lynch AM, Robinson J. Exposures to e-cigarettes and their refills: calls to Australian Poisons Information Centres, 2009–2016. The Medical Journal of Australia. 2019 Jan 28;210(3):126.
[8] Centers for Disease Control and Prevention. Calls to Poison Centers for Exposures to Electronic Cigarettes — United States, September 2010–February 2014 2014. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6313a4.htm?s_cid=mm6313a4_w
[9] Vardavas CI, Girvalaki C, Filippidis FT, Oder M, Kastanje R, de Vries I, et al. Characteristics and outcomes of e-cigarette exposure incidents reported to 10 European Poison Centers: a retrospective data analysis. Tobacco Induced Diseases. 2017;15(1):36

A case study in Korea proved that unintentional nicotine ingestion in infants can be fatal[10]. The same case study also points out that misunderstanding and misuse of the e-liquids accounted for more than half of adverse events related to e-cigarettes reported by the Korean Consumer Injury Surveillance System from January 2012 to April 2015. Ingestion of nicotine at low to moderate toxic dose can result in a range of signs and symptoms, including burning sensation in the mouth and throat, nausea, vomiting, and confusion. Higher doses are associated with arrhythmias, bradycardia, convulsions, coma, respiratory failure, rapid progression to hypotension, and death[11]. A lethal dose of nicotine in children is estimated to be 1mg/kg[12].

Currently, there is no regulation to ensure the quality control and production standards of e-cigarettes. The lack of child resistant closures for nicotine e-liquid containers is a significant concern of the RACP. We support extending the requirement for child-resistant packaging stipulated in Therapeutic Goods Order No. 95 (TGO95) to all liquid nicotine products (whether approved or unapproved) to prevent or reduce accidental poisonings. Imposing such a requirement can also be used as an avenue to improve poor-quality control in e-cigarette product packaging.

2. Comments on ACCS-ACMS's Advice

a) Risks and benefits of the use of a substance

Nicotine e-cigarettes might have a role in smoking cessation or tobacco harm reduction, but the current evidence is unable to conclude this. Several harms associated with their use have been highlighted in literature.

Potential Benefits	Evidence
Smoking Cessation	Evidence on the effectiveness of e-cigarettes as a viable tool for smoking cessation to date remains limited and inconsistent. It is widely agreed that more robust and thorough studies are urgently required to fill the evidence gap. For those smokers who seek assistance in quitting, the RACP advocates for the proven and well regulated smoking cessation technologies, including pharmacotherapies, ahead of vaping. A 2018 randomised controlled trial found that the 1-year abstinence rate was 18.0% in the e-cigarette group, as compared with 9.9% in the nicotine-replacement group when both groups had regular face-to-face meetings with clinicians. However, the study also pointed out that the rate of continuing e-cigarette use was substantially higher – around 80% after 1 year among those who were tobacco abstinent[13], indicating that people were simply replacing tobacco cigarettes with e-cigarettes rather than ceasing smoking altogether. A 2020 review of 13 studies concluded that e-cigarette use does not lead to significant increase in smoking cessation among smokers. The difference in smoking cessation was found to be similar among e-cigarette users compared with non–e-cigarette users. The pattern of use had an impact on outcomes for e-cigarette users. The study found that smokers who use e-cigarettes daily for at least a month were more likely to quit smoking compared with those who use e-cigarettes intermittently[14]

[10] Seo AD, Kim DC, Yu HJ et al. Accidental ingestion of E-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. Korean journal of pediatrics. 2016 Dec;59(12):490.
[11] Seo AD, Kim DC, Yu HJ et al. Accidental ingestion of E-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. Korean journal of pediatrics. 2016 Dec;59(12):490.
[12] Seo AD, Kim DC, Yu HJ et al. Accidental ingestion of E-cigarette liquid nicotine in a 15-month-old child: an infant mortality case of nicotine intoxication. Korean journal of pediatrics. 2016 Dec;59(12):490.
[13] Hajek P, Phillips-Waller A, Przulj D, et al. A randomized trial of e-cigarettes versus nicotine-replacement therapy. N Engl J Med. 2019;380(7):629-637.
[14] Patil S, Arakeri G, Patil S, et al. Are electronic nicotine delivery systems (ENDs) helping cigarette smokers quit?-Current evidence. J Oral Pathol Med. 2020;49(3):181-189

A recent Cochrane review of 50 studies concluded that there was moderate-certainty evidence that nicotine e-cigarettes increase smoking cessation rates at six months or longer compared to non-nicotine e-cigarettes and nicotine replacement therapy, but the finding is limited by imprecision arising from the small number of randomised controlled trials. There was very low-certainty evidence showing that nicotine e-cigarettes increased smoking cessation rates compared to behavioural support alone or no support. The need for more studies to ascertain the extent of effect, particularly when using modern e-cigarette products is highlighted in the review[15].

The literature review conducted by the Thoracic Society of Australia and New Zealand (TSANZ)[16] found that reports from the National Academies of Sciences, Engineering and Medicine (NASEM), Commonwealth Scientific and Industrial Research Organisation (CSIRO), and the National Health and Medical Research Council (NHMRC) all have concluded that the evidence on e-cigarettes as an effective smoking cessation aid is limited and that whether they are more or less superior than conventional smoking cessation aids or no treatment is unclear.

One of the conclusions drawn from the 2020 US Surgeon General's report is that e-cigarettes are continually evolving and heterogenous products used in different ways, meaning the efficacy of a particular e-cigarette product demonstrated in clinical trials cannot draw generalisations. The report also found that there is insufficient evidence to conclude that e-cigarettes, in general, increase smoking cessation at this point in time. Approved smoking cessation medicines, in conjunction with behavioural counselling are cost effective smoking cessation modalities[17].

The 2020 Australian summary report did not find nicotine e-cigarettes to be more effective than no intervention, non-nicotine e-cigarettes, or nicotine replacement therapy in aiding smoking cessation. It found that nicotine e-cigarettes contribute to prolonged nicotine use[18]. The summary report also highlights that:

- Reviews and large-scale cross-sectional studies suggest a softening of the smoking population over time – declining smoking prevalence has generally been accompanied by increasing motivation to quit, reduced dependency and greater quit rates among smokers. Only about 2% of adults aged 18 or over were smokers who were unmotivated or unable to quit in Australia.
- The concept of the "hardening hypothesis" - that as smoking prevalence decreases, the remaining smokers will be less willing to stop smoking should be dismissed, and be substituted with the evidence based conclusion that there is "softening" of the smoking population, who become more readily able to quit.

It is worth noting that most smokers quit smoking unassisted[19].

Although there is data revealing declines in smoking rates in countries similar to Australia, the first time series analysis based on repeated cross-sectional population surveys in the UK revealed no clear relationship between e-cigarette use and smoking reduction in the UK between 2006 and 2016. The study thus

[15] Cochrane database of systemic reviews: electronic e-cigarettes for smoking cessation. 2020. Available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD010216.pub4/full
[16] Electronic cigarettes: A position statement from the Thoracic Society of Australia and New Zealand. 2020. Available at: https://onlinelibrary.wiley.com/doi/full/10.1111/resp.13904
[17] US Surgeon General Report: Smoking Cessation. 2020. Available at: https://www.hhs.gov/sites/default/files/2020-cessation-sgr-executive-summary.pdf
[1818] Australian National University. Summary report on use of e-cigarettes and relation to tobacco smoking uptake, smoking cessation, relevant to Australian context. Available at: https://openresearch-repository.anu.edu.au/bitstream/1885/211618/3/E-cigarettes%20smoking%20behaviour%20summary%20report%20final%20200924.pdf
[19] Greenhalgh EM, Stillman S, Ford C. Tobacco in Australia: Facts and Issues: 7.6 How smokers go about quitting, 2016. Available at: http://www.tobaccoinaustralia.org.au.

	concluded that if e-cigarette use had contributed to reduced smoking consumption, the effect was likely to be very small at a population level[20].
Harm Reduction	There is evidence indicating that there are immediate health benefits for individuals switching from tobacco smoking to e-cigarettes, however the degree of harm reduction cannot be quantified[21] and long term health impacts are not known. A few studies found a significant reduction in smokers' levels of urinary metabolised acrolein and benzene as well as exhaled carbon monoxide after switching to e-cigarettes[22] [23]. This finding suggested that switching from tobacco to e-cigarettes may be associated with a decline in exposure to selected toxicants and carcinogens otherwise present in tobacco cigarettes[24]. E-cigarettes are not without the potential to cause harm[25] and their labelling as a 'harm reduction' methodology has impacted the perceptions of adolescents and young people who view vaping as far less harmful or even harmless in comparison to tobacco cigarettes[26]. A low-powered cross-sectional study showed that e-cigarette use may deliver similar nicotine levels as tobacco cigarettes and is also linked to reduced exposure to known tobacco-related carcinogens and toxins. However, these benefits are not associated with dual use of e-cigarettes and tobacco cigarettes. It therefore suggests that the potential benefits of e-cigarettes can only be realised provided there is full cessation of tobacco smoking[27]. Otherwise, there is little to no beneficial impact on health risk and effects, as outlined by the WHO[28].

[20] Beard E, Brown J, Michie S, et al. Is prevalence of e-cigarette and nicotine replacement therapy use among smokers associated with average cigarette consumption in England? A time-series analysis. BMJ Open 2018; 8: e016046.
[21] NHMRC CEO Statement: E-cigarettes. 2017. Available from: https://www.nhmrc.gov.au/about-us/resources/ceo-statement-electronic-cigarettes
[22] McRobbie H, Phillips A, Goniewicz ML, Smith KM, Knight-West O, Przulj D, Hajek P. Effects of switching to electronic cigarettes with and without concurrent smoking on exposure to nicotine, carbon monoxide, and acrolein. Cancer Prevention Research. 2015 Sep 1;8(9):873-8.
[23] Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, Benowitz NL. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. Nicotine & Tobacco Research. 2017 Feb 1;19(2):160-7.
[24] Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, Benowitz NL. Exposure to nicotine and selected toxicants in cigarette smokers who switched to electronic cigarettes: a longitudinal within-subjects observational study. Nicotine & Tobacco Research. 2017;19(2):160-
25 Sohal SS, Eapen MS, Naidu VGM, et al. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ Open Res 2019; 5:00159-2018 [https://doi.org/10.1183/23120541.00159-2018
26 Substance Abuse and Mental Health Services Administration (SAMHSA): Reducing Vaping Among Youth and Young Adults. SAMHSA Publication No. PEP20-06-01-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2020
[27] Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, et al. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users A Cross-sectional Study E-Cigarettes and Toxin Exposure. Annals of internal medicine. 2017;166(6):390-400
[28] WHO Report on the Global Tobacco Epidemic, 2019. Geneva: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

Potential Harms	Evidence
Adverse Health Impacts	Evidence reveals that e-cigarette use is not without adverse health impacts. A study in 2016 suggested that nicotine-containing e-cigarettes are linked to an elevated risk of aortic stiffness and increased blood pressure in young smokers[29]. A systematic review of case reports found that e-cigarettes can have a negative impact on respiratory, gastrointestinal, cardiovascular, neurological and immune systems[30]. Experimental data suggest that e-cigarettes can induce lung inflammation, a hallmark for the development of lung cancer and chronic obstructive pulmonary disease (COPD), though much less than tobacco smoking[31]. A 2019 study demonstrated that exposure to heat-not-burn tobacco products has the same detrimental effect as tobacco cigarettes and e-cigarettes on human lung cells in vitro[32]. There is a dearth of long-term e-cigarette exposure studies in humans, restricting our understanding of its direct effects on disease development and progression[33]. Further research is urgently needed to understand their long-term health impacts. that a reduction in the levels of some potentially dangerous chemicals. This also needs to be considered in light of the new set of chemicals that present an as yet to be fully identified and characterised range of possible health risks when heated or burned, inhaled deep into the lungs.
Youth Vaping	Growth of e-cigarette use among youth has increased the most in in countries which have liberalised the e-cigarette market. In the US, e-cigarettes have been the most commonly used tobacco products among young people since 2014[34]. A US survey found that the number of secondary students who had vaped in past 30 days doubled from 2017 to 2019. [35] A recent US Morbidity and Mortality Weekly report revealed that 27.5% of high school students were current e-cigarette users and 73.4% of high school students had observed e-cigarette use on campus in 2019. This increase occurred with the rising popularity of pod mods, which usually use nicotine salts to allow easier inhalation of high level of nicotine with less irritation to throat[36]. Roughly 1,000 vaping products were confiscated from 25 high schools in California and North Carolina during the 2018–19 academic year[37]. In the US, the impact of a more liberalised regulatory environment can be seen as many young people view vaping as socially acceptable[38].

[29] Vlachopoulos C, Ioakeimidis N, Abdelrasoul M,et al. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. Journal of the American College of Cardiology. 2016;67(23):2802-3
[30] Talbot P. Potential health effects of electronic cigarettes: A systematic review of case reports. Preventive medicine reports. 2016;4:169-78
[31] Shields PG, Berman M, Brasky, et al. A review of pulmonary toxicity of electronic cigarettes in the context of smoking: A focus on inflammation. Cancer Epidemiology and Prevention Biomarkers. 2017.
[32] Sohal SS, Eapen MS, Naidu VG, et al. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ open research. 2019 Feb 1;5(1).
[33] Sohal SS, Eapen MS, Naidu VG, et al. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ open research. 2019 Feb 1;5(1).
[34] CDC Data and Statistics: Youth and Tobacco use. Available at: https://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/tobacco_use/index.htm
[35] Miech R, Johnston L, O'Malley PM, et al. Trends in adolescent vaping, 2017–2019. N Engl J Med 2019; 381: 1490–91.
[36] CDC. US Morbidity and Mortality Weekly report. Characteristics of E-cigarette, or Vaping, Products Confiscated in Public High Schools in California and North Carolina — March and May 2019 . October 2020. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6942a7-H.pdf
[37] CDC. US Morbidity and Mortality Weekly report. Characteristics of E-cigarette, or Vaping, Products Confiscated in Public High Schools in California and North Carolina — March and May 2019 .October 2020. Available at: https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm6942a7-H.pdf
[38] Substance Abuse and Mental Health Services Administration (SAMHSA): Reducing Vaping Among Youth and Young Adults. SAMHSA Publication No. PEP20-06-01-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2020

A Canadian survey found 20% of students had used e-cigarettes in the past 30 days between 2018 and 2019, an increase from 10% in 2016-17[39].

In the UK, the prevalence of ever use of e-cigarettes among young people aged 11 to 15 years old was 25% in 2018, the same as in 2016, but an increase compared to 2014[40]. Current e-cigarette use increases with age – ranging from less than 1% of young people aged 11 to 11% of young people aged 15[41]

In Aotearoa New Zealand, a cross sectional survey showed that the number of students aged 14-15 who had ever tried e-cigarettes (37.3%) outnumbered that of who had ever smoked (19.6%) in 2019[42]

In Australia, the 2019 National Drug Strategy Household Survey (NDSHS) has found that roughly two-thirds of current smokers and 1 in 5 non-smokers aged 18–24 reported having tried e-cigarettes[43].

A recent paper by the Substance Abuse and Mental Health Services Administration (SAMHSA) in the US on reducing vaping amongst youth and young adults[44] outlined the following challenges in relation to preventing youth vaping:

- Access and availability of vaping products – despite a federal law being passed in December 2019, to raise the federal legal age to purchase tobacco, including e-cigarettes, to 21, youths are able to obtain vaping products either online or from stores without age verification. In addition, sharing devices and getting older friends or siblings to purchase them was common.

- Marketing that targets young people – marketing aimed at youth (including flavouring) and sponsorship of youth focused events normalises vaping and vaping devices are able to advertise on television, in movies, magazines, newspapers, social media, and other mediums.

- Perception of vaping as low risk to health – because there is no combustion, youth see vaping as far less harmful or even harmless in comparison to tobacco cigarettes.

- Use of vaping products in public places – while some states in the US include vaping under smoke/tobacco free laws, other states do not, and this creates confusion. This leads to people vaping in designated smoke/tobacco free areas, one study noting[45] 60% of people who vape

[39] Summary of results for the Canadian Student Tobacco, Alcohol and Drugs Survey. Available at: https://www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2018-2019-summary.html
[40] NHS digital data. Smoking, Drinking and Drug Use among Young People in England 2018. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/smoking-drinking-and-drug-use-among-young-people-in-england/2018
[41] NHS digital data. Smoking, Drinking and Drug Use among Young People in England 2018. Available at: https://digital.nhs.uk/data-and-information/publications/statistical/smoking-drinking-and-drug-use-among-young-people-in-england/2018
[42] Walker N, Parag V, Wong SF et al. Use of e-cigarettes and smoked tobacco in youth aged 14–15 years in New Zealand: findings from repeated cross-sectional studies (2014–19). The Lancet Public Health. 2020 Jan 22.
[43] National Drug Strategy Household Survey 2019. Chapter 2: Tobacco Smoking. Available at: https://www.aihw.gov.au/getmedia/3564474e-f7ad-461c-b918-7f8de03d1294/aihw-phe-270-NDSHS-2019.pdf.aspx?inline=true
[44] Substance Abuse and Mental Health Services Administration (SAMHSA): Reducing Vaping Among Youth and Young Adults. SAMHSA Publication No. PEP20-06-01-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2020
[45] Shi, Y., Cummins, S. E., Zhu, S. (2017). Use of Electronic Cigarettes in Smoke-Free Environments. Tobacco Control, 26(e1), e19–e22.

	doing so in smoke free areas such as restaurants, movie theatres and shopping malls. • Regulatory environment – in the US, while the Food and Drug Administration (FDA) has federal regulatory authority over e-cigarettes and vaping devices, states and local jurisdictions may also have the authority to pass policies to reduce access to, and availability of, these products. Because of this complicated environment, evidence-based approaches to policy to ensure rates of youth vaping are minimised are needed. • Cultural considerations – the social relationships that develop a culture of vaping, such as sharing and borrowing devices and the element of peer group pressure all add to the embedding and normalisation of the behaviour. YouTube channels and social media dedicated to vaping are proliferating.
Renormalising smoking	There is concern over the renormalisation of smoking in the form of e-cigarettes. This concern is heightened by the fact that many e-cigarette products are promoted in ways that glamourise smoking[46]. A wide range of advertising and marketing strategies have been used to particularly target the youth market, including production innovation and celebrity endorsement[47].
Gateway effect	The potential gateway effect of e-cigarettes is a major concern as several studies have associated teen vaping with elevated risk of cigarette initiation[48] [49] [50]. The 2018 NASEM report also finds substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults[51]. E-cigarette use by young people is unsafe, even if they do not progress to cigarette smoking. The Tackling Indigenous Smoking program for Aboriginal and Torres Strait Islander peoples has successfully shown that fewer Aboriginal and Torres Strait Islander young people are taking up smoking than ever before. The Talking About Smokes Survey shows that around 21% of Aboriginal and Torres Strait Islander smokers have tried e-cigarettes, and those people tend to be: • younger • living in non-remote areas or more advantaged areas • daily smokers • wanting to quit, having made a quit attempt/used NRT in the past year. The Tackling Indigenous Smoking Program has raised concerns about e-cigarettes introducing a new pathway to harmful and addictive behaviour[52]. The Canadian student tobacco, alcohol, and drug survey 2018-19 found that nicotine e-cigarettes are commonly used in students who vaped in the past 30 days – of all those students, 42 per cent were never smokers. Among students

[46] Benowitz NL, Goniewicz ML. The regulatory challenge of electronic cigarettes. The Journal of the American Medical Association. 2013;310(7):685-6.
[47] US Department of Health and Human Services. E-cigarette use among youth and young adults: A report of the Surgeon General. Chapter 4: Activities of the E-Cigarette Companies. Available at: https://www.ncbi.nlm.nih.gov/books/NBK538679/
[48] Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. Jama. 2015 Aug 18;314(7):700-7.
[49] Coleman BN, Apelberg BJ, Ambrose BK, et al. Association Between Electronic Cigarette Use and Openness to Cigarette Smoking Among U.S. Young Adults. Nicotine & Tobacco Research. 2015;17(2):212-8
[50] Barrington-Trimis JL, Urman R, Berhane K, et al. E-cigarettes and future cigarette use. Pediatrics. 2016;138(1):e20160379
[51] National Academies of Sciences, Engineering. Public Health Consequences of E-Cigarettes. Available at: https://www.ncbi.nlm.nih.gov/books/NBK507163/
[52] Tackling Indigenous Smoking: E-cigarettes. Available at: https://tacklingsmoking.org.au/e-cigarettes/

	who had tried both cigarettes and vaping products, 41 per cent experimented with an e-cigarette first and 47 per cent experimented with a tobacco cigarette first[53]. However, a 2020 systematic review found that evidence from more recent studies is conflicting. While temporal analysis revealed that increasing e-cigarette use in the US was associated with a faster decline in tobacco smoking, two other studies showed that adolescents who used e-cigarettes were more likely to progress to tobacco cigarette smoking [54]. A recent Australian report[55] using a meta-analysis of data showed that never smokers who have used e-cigarettes were, on average three times more likely to try and progress to tobacco smoking than those who have not used e-cigarettes. All studies found evidence of an increased risk of varying magnitude. Where information on types of e-cigarettes is available, nicotine e-cigarettes were the subject of research in the majority of these studies.
Nicotine dependence and addiction	E-cigarette use is highly likely to lead to nicotine addiction. There is evidence showing that e-cigarettes can deliver similarly rapid onset levels of nicotine as that obtained from tobacco cigarettes[56]. The addiction potential for these products are linked to the speed of nicotine delivery, which are influenced by e-liquid components, device characteristics and use behaviour (e.g. a user's puff volume, puffing rate, and depth of inhalation)[57]. Studies have shown that children develop nicotine dependence, even at low levels of consumption within days of starting to smoke, and so the uptake of nicotine-containing e-cigarettes among youth and adolescents is a cause for serious concern[58].
Exposure to known toxicants	An array of known human carcinogens and toxins has been found in e-cigarette aerosols, cartridge, and refill liquids[59] [60]. The toxic chemicals identified include tobacco specific nitrosamines (TSNA), volatile organic compounds (VOCs), heavy metals, aromatic hydrocarbons (PAHs) as well as carcinogenic aldehyde and carbonyl compounds, all known to have adverse health effects. Recent research has warned that flavourings combined with solvents in e-cigarettes can form toxic chemicals that lead to breathing, heart and blood vessel problems[61].
Safety and quality	Presently, e-cigarettes are largely unregulated products. Some safety issues have been reported due to the lack of quality control and standards: • Incorrect nicotine concentration labelling[62]

[53] Summary of results for the Canadian Student Tobacco, Alcohol and Drugs Survey. Available at: https://www.canada.ca/en/health-canada/services/canadian-student-tobacco-alcohol-drugs-survey/2018-2019-summary.html
[54] Bozier J, Chivers EK, Chapman DG, et al. The Evolving Landscape of e-Cigarettes: A Systematic Review of Recent Evidence. *Chest*. 2020;157(5):1362-1390.
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[56] St Helen G, Havel C, Dempsey DA, et al. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction (Abingdon, England). 2016;111(3):535-44
[57] DeVito E, Krishnan-Sarin S. E-cigarettes: Impact of E-Liquid Components and Device Characteristics on Nicotine Exposure. Current neuropharmacology. 2017
[58] RACP policy on e-cigarettes 2018. Available at: https://www.racp.edu.au/docs/default-source/advocacy-library/policy-on-electronic-cigarettes.pdf
[59] Ioakeimidis N, Vlachopoulos C, Tousoulis D. Efficacy and safety of electronic cigarettes for smoking cessation: a critical approach. Hellenic Journal of Cardiology. 2016;57(1):1-6
[60] Cheng T. Chemical evaluation of electronic cigarettes. Tobacco control. 2014;23(suppl 2):ii11-ii7; Pisinger C. A systematic review of health effects of e-cigarettes. Denmark; 2015
[61] Jordt SE, Caceres AI, Jabba S. Flavor-Solvent Adducts in Electronic Cigarette Liquids Are Modulators of Respiratory Irritant Receptors with Distinct Toxicological Effects on Lung Epithelial Cells. In A50 Molecular mechanisms of environmental and occupational lung diseases 2019 may (pp. a7312-a7312). American thoracic society.
[62] Yang L, Rudy SF, Cheng JM, et al. Electronic cigarettes: incorporating human factors engineering into risk assessments. Tobacco control. 2014;23(suppl 2):ii47-ii53

- Variation in the composition and concentrations of e-liquids, across and within brands[63].
- Explosion of the batteries, e-liquid leaking, and operational risks, resulting in burns or poisoning in children[64].

b) Purposes for which a substance is to be used and the extent of use of a substance

The RACP supports the intent of the TGA's proposal to regulate nicotine e-cigarettes as a prescription only medicine, confining their access to smokers who are unable to quit smoking via other approved methods. Yet, we emphasise that the ultimate aim of smoking cessation support provided by medical practitioners should be helping patients overcome their nicotine addiction.

In our view, not smoking tobacco or using e-cigarettes remain the safest options for the community. For those seeking to quit smoking, the RACP advocates for the TGA approved smoking cessation products. Approved nicotine replacement treatment in various forms has been an important and effective modality to facilitate smokers to quit smoking and relieve some of nicotine withdrawal symptoms. In the face of contradictory evidence on many aspects of e-cigarettes, the principles of the precautionary approach and reasonable safety should be applied and take precedence. Thus, on this matter, the RACP strongly supports the precautionary approach taken by the TGA.

c) Toxicity of nicotine

Nicotine itself is highly addictive, comparable to heroin and cocaine [65]. The use of nicotine not only causes addiction, but also adversely affects major body organs such as the heart, reproductive system, and lungs [66]. Nicotine is also harmful to the developing brain; children and adolescents are more sensitive to the harmful effects of nicotine and the risk of nicotine addiction[67].

Given the toxicity of nicotine, the RACP advises that nicotine should not be prescribed to those aged less than 18 years and other high-risk population groups for which nicotine is shown to be harmful, such as pregnant women.

d) Dosage, formulation, labelling, packaging and presentation of a substance

The e-cigarette retail market has continued to evolve and diversify rapidly, with different models and a wide range of flavours available. Despite this, e-cigarettes are subject to differing quality control processes and labelling requirements, and there is a variation in the composition and concentrations of e-liquids, across and within brands[68]. There is evidence indicating that e-cigarette product labelling and packaging provided inadequate or misleading information about product contents, use and warnings[6970]

As such, the RACP recommends the TGA to establish appropriate quality and safety standards for e-cigarette products and enforce the packaging and labelling requirements, including disclosure of all

[63] Buonocore F, Gomes ACM, Nabhani-Gebara S, et al. Labelling of electronic cigarettes: regulations and current practice. Tobacco control. 2017;26(1):46-52
[64] Yang L, Rudy SF, Cheng JM, et al. Electronic cigarettes: incorporating human factors engineering into risk assessments. Tobacco control. 2014;23(suppl 2):ii47-ii53..
[65] World Health Organization. Gender, women, and the tobacco epidemic 2010 [137-49]. Available at: http://www.who.int/tobacco/publications/gender/en_tfi_gender_women_addiction_nicotine.pdf
[66] Mishra A, Chaturvedi P, Datta S, et al. Harmful effects of nicotine. Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology. 2015;36(1):24
[67] Goriounova NA, Mansvelder HD. Short- and long-term consequences of nicotine exposure during adolescence for prefrontal cortex neuronal network function. Cold Spring Harbor perspectives in medicine. 2012;2(12):a012120
[68] Buonocore F, Gomes ACM, Nabhani-Gebara S, et al. Labelling of electronic cigarettes: regulations and current practice. Tobacco control. 2017;26(1):46-52.; FDA. Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted By FDA, 2014; Etter JF, Zäther E, Svensson S. Analysis of refill liquids for electronic cigarettes. Addiction (Abingdon, England). 2013;108(9):1671-9.
[69] Yang L, Rudy SF, Cheng JM, et al. Electronic cigarettes: incorporating human factors engineering into risk assessments. Tobacco control. 2014;23(suppl 2):ii47-ii53
[70] Buonocore F, Gomes ACM, Nabhani-Gebara S, et al. Labelling of electronic cigarettes: regulations and current practice. Tobacco control. 2017;26(1):46-52

ingredients and their concentrations in e-liquid, child-resistant packaging, plain packaging rules and health warning labels.

e) Potential for misuse of a substance

Considering that e-cigarettes can deliver similarly rapid onset levels of nicotine as that obtained from tobacco cigarettes, e-cigarette users can become addicted to nicotine in a manner comparable to tobacco cigarette smokers.

Another potential for misuse is vaping of other drugs. The outbreak of vaping related lung illness (or EVALI) in the United State in 2019 illustrated that e-cigarette use is not confined to nicotine, but being used to consume cannabis among young people. Due to the illegal status of cannabis, cannabis e-liquids are unregulated and do not undergo any toxicological and clinical assessment[71]. The US Centers for Disease Control and Prevention (CDC) has warned against adding additional substances that are not intended by the manufacturer to e-cigarette products and warned against the use of THC containing e-cigarettes to avoid potentially harmful effects[72].

As of February 2020, there was a total of 2807 reported EVALI cases or death, with [73]. Although vitamin E acetate was identified as a primary cause, the US CDC highlights that evidence is not sufficient to exclude the contribution of other chemicals of concern in some of these injuries[74]. A study points out that before the EVALI outbreak, there were already at least 30 reports of lung illnesses linked to e-cigarettes in the literature, starting from 2012. A wide range of lung conditions were highlighted in these reports, encompassing organizing pneumonia and diffuse alveolar damage to interstitial lung disease[75].

Although the proposed interim decision is to clarify nicotine e-cigarette regulation, it does not control the types of substances users add and inhale, the strength of nicotine in e-liquids, as well as the characteristics of e-cigarette devices. We would like to underline the fact that both the composition of e-liquids and e-cigarette device characteristics affect the toxicity of the e-cigarette aerosol[76].

f) Any other matters that the Secretary considers necessary to protect the public health

To date, no e-cigarette device (regardless of nicotine content) has been approved by the Therapeutic Goods Administration (TGA) for use to aid smoking cessation – any therapeutic and toxicity claims made about e-cigarettes (with or without nicotine) must be supported by transparent, high quality studies and have undergone the TGA's review processes and secured their approval. If access to e-cigarettes become available on prescription to smokers, the RACP recommends that the use of e-cigarettes should be banned in all areas that are designated to be smoke-free by Australia's state and territory laws, in a bid to protect youths and non-smokers.

It is worrying to see a significant increase in vaping among Australian teens[77] when the sale and use of e-cigarettes is currently against the law. The RACP is significantly concerned that any easing of access restrictions would be a contributing factor to ongoing and alarming increases in vaping amongst teens, which is currently seen in jurisdictions such as the US and Canada. Youth access through illegal retailer

[71] Giroud C, de Cesare M, Berthet A, Varlet V, Concha-Lozano N, et al. E-cigarettes: A review of new trends in cannabis use. International Journal of Environmental Research and Public Health, 2015; 12(8):9988–10008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26308021
[72] CDC. Outbreak of Lung Injury Associated with the use of E-cigarettes, or Vaping, Products. Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
[73] CDC. Outbreak of Lung Injury Associated with the use of E-cigarettes, or Vaping, Products. Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
[74] CDC. Outbreak of Lung Injury Associated with the use of E-cigarettes, or Vaping, Products. Available at: https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html
[75] Stanbrook MB, Drazen JM. Vaping-Induced Lung Disease—A Look Forward by Looking Back.
[76] Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). Tobacco control. 2016;25(Suppl 2):ii81-ii7

sales[78] or through legal purchasers inside their social circles[79] e.g. peers, relatives or strangers must be prevented.

Global tobacco companies, such as British American Tobacco, Imperial Tobacco, Reynolds American Inc. and Lorillard, have now either established or acquired e-cigarettes as part of their product line[80]. In light of this development, it is important for us to remain mindful of the tobacco industry's historical tactics and attempts to influence and resist tobacco control policy[81]. The RACP maintains that e-cigarette and tobacco industries must not be involved in the design of e-cigarette regulatory framework and the associated implementation in Australia. These industries are not experts in health policy; there are major conflicts between their vested commercial interests and public health. We call on the TGA to put in place measures to prohibit marketing tactics such as messaging and commercial strategy used by tobacco and e-cigarette industries aiming at prescribing doctors to increase the sale of nicotine e-cigarettes.

Additional considerations

Additional considerations warrant further investigation from the TGA prior to implementing the proposed regulatory change.

The potential medico-legal, ethical and professional responsibilities for the medical profession in taking on the prescribing role for a product unapproved by the TGA as a therapeutic product for smoking cessation, taking essentially a 'gatekeeper role' in lieu of regulation, involves risks to be considered. The prescribing of commercial products outside usual standards of required scientific evidence of safety and effectiveness for a claimed therapeutic purpose which doctors have no high-quality knowledge to base any such prescribing decisions is a risk.

The RACP notes that as part of the implementation plan of this proposal, the TGA plans to develop prescribing guidelines for e-cigarettes for medical practitioners. We are supportive of the guideline development. However, there needs to be full consideration of the feasibility and quality of any prescribing guidelines when the current evidence base is insufficient to inform which nicotine e-cigarettes to recommend as well as the doses, frequency and prescription duration. Given the vast range of commercial e-cigarette products on the market and the product marketing attached to these products, with unknown quality and safety standards, and no evidence of effectiveness to aid quitting. The current evidence base is insufficient to inform which nicotine e-cigarettes to recommend as well as the doses, frequency and prescription duration. We question how appropriate guidelines will be developed without robust scientific evidence. Without such high-quality data, we are concerned that medical practitioners do not have appropriate evidence and expertise to inform prescribing decisions. This also should be considered in light of the RACP commitment to identifying and disinvesting in low value and harmful, or potentially harmful, clinical interventions such as through the *Evolve* initiative https://evolve.edu.au/.

Further, misperceptions of relative risk and safety of e-cigarette use may lead to their use in pregnancy as well as shared and borrowed e-cigarette use, especially among young people. Thus, the RACP recommends the inclusion of a specific counselling point on not sharing prescribed medication and cessation of e-cigarette use during pregnancy in the prescribing guidelines. These recommendations are not currently contained in the RACGP Supporting smoking cessation: A guide for health professionals (Recommendation 15: nicotine e-cigarettes).

[78] FDA News. FDA takes new steps to address epidemic of youth e-cigarette use, including a historic action against more than 1,300 retailers and 5 major manufacturers for their roles perpetuating youth access. Available at: https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-address-epidemic-youth-e-cigarette-use-including-historic-action-against-more
[79] Substance Abuse and Mental Health Services Administration (SAMHSA): Reducing Vaping Among Youth and Young Adults. SAMHSA Publication No. PEP20-06-01-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory, Substance Abuse and Mental Health Services Administration, 2020
[80] Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation*. 2014;129(19):1972-1986. doi:10.1161/CIRCULATIONAHA.114.007667
[81] Grana RA, Benowitz N, Glantz SA. Background Paper on E-cigarettes (Electronic Nicotine Delivery Systems). WHO Tobacco Control Papers. 2013.

The RACP would recommend allowing for capturing more of the growing evidence base and in particular the results from the NHMRC review currently underway. Australia has seen a steady decline in daily tobacco smoking since 1991[82], with a substantial decline from 2016 to 2019. If the trend continues, this means that the balance of harm and benefit with regard to nicotine e-cigarette use will continually change as a result.

[82] AIHW. Alcohol, tobacco & other drugs in Australia. 2020. Available at: https://www.aihw.gov.au/reports/alcohol/alcohol-tobacco-other-drugs-australia/contents/drug-types/tobacco