Australian Government
National Health and Medical Research Council

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2022 CEO Statement on Electronic Cigarettes: Administrative Report

June 2022

NHMRC

Contents

Refer to documents

This administrative report refers to the development of the *2022 CEO Statement on Electronic Cigarettes* (CEO Statement) and the following documents:

- *Inhalation toxicity of non-nicotine e-cigarette constituents: risk assessments, scoping review and evidence map (toxicology report)*
- *Effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs, perception, intentions, and behaviours: a mixed-methods systematic review*
- *E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis*
- *Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review*
- *Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*
- *Electronic cigarettes and health outcomes: systematic review of the global evidence*
- *Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure*
- *CEO Statement on Electronic Cigarettes, including:*
  - *Plain English summary*
  - *Supporting infographics*

Introduction

The National Health and Medical Research Council (NHMRC) CEO Statement on Electronic Cigarettes provides public health advice on the safety and impacts of electronic cigarettes (e-cigarettes) based on review of the current evidence. In April 2020, the Australian Government Department of Health commissioned NHMRC to update the 2017 CEO Statement.

NHMRC first released the CEO Statement on Electronic Cigarettes in 2015. This Statement was developed in consultation with, and supported by, Australian federal, state and territory Chief Health/Medical Officers. In 2017, the CEO Statement was updated with the latest available evidence. The 2017 CEO Statement concluded that:

- there was insufficient evidence to support claims that e-cigarettes were safe
- further research was needed to enable to long-term safety, quality and efficacy of e-cigarettes to be assessed
- until such evidence was produced, health authorities and policy-makers should act to minimise harm to users and other vulnerable groups.

The intent of the CEO Statement is to ensure that Australians are provided with the most up-to-date information on the safety and potential health implications of e-cigarettes and the impact of sponsorship, advertising and promotion of e-cigarettes. The updated CEO Statement summarises the evidence on the safety and quality of electronic cigarettes (e-cigarettes) and

their efficacy for smoking cessation. The CEO Statement has been informed by an evaluation of the latest and best available scientific evidence.

Contributors

NHMRC project team

The review was undertaken by the Public Health Section of the Research Translation Branch.

Current project team

- Jennifer Savenake: Director, Public Health Team
- Michelle Crino: Assistant Director, Public Health Team (from April 2021)
- Bethany Corr: Senior Project Officer, Public Health Team.

Previous NHMRC project team members

- Joanna Bencke: Assistant Director Public Health Team (to March 2021)

Contractors

Evidence Reviewers

The following contractors were commissioned to conduct evidence reviews that underpinned the updated CEO Statement:

The George Institute for Global Health (TGI)

- *Effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs, perception, intentions, and behaviours: a mixed-methods systematic review*

The National Centre for Epidemiology and Population Health (NCEPH)

NCEPH were contracted by the Australian Government Department of Health to produce the following evidence reviews:

- *E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis*
- *Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review*
- *Electronic cigarettes and health outcomes: systematic review of the global evidence*

These reviews were also used by NHMRC, with additional requirements being procured directly with NCEPH:

- *Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*
- *Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure.*

The evidence review teams completed a declaration of interest process before being appointed by NHMRC. No conflicts of interest were identified that needed to be managed.

Independent Methodological Reviewers

The following agencies were contracted to conduct independent methodological reviews on evidence reviews and reports used to underpin the CEO Statement as part of NHMRC quality assurance processes:

- HealthConsult Pty Ltd
- Cochrane Australia.

All methodological reviewers completed a declaration of interest process before being appointed by NHMRC. No conflicts of interest were identified that needed to be managed.

Independent Expert Reviewers

Expert reviewers conducted independent peer review of the CEO Statement as part of NHMRC quality assurance processes.

The independent expert reviewers were:

- Professor Richard Edwards
- Associate Professor Coral Gartner
- Associate Professor Alexander Larcombe.

Governance

The Australian Government Department of Health Commissioned NHMRC to update the 2017 CEO Statement and contributed funding for expenses relating to evidence evaluations, methodological reviews, committee costs and part of the NHMRC's Public Health team staffing costs. NHMRC provided funding for additional staffing costs, the toxicology report (including methodological review), CEO Statement infographics and publication costs. All draft research protocols and evidence review reports were considered and advised on by the Committee in line with its Terms of Reference. The Committee advised on the development of the CEO Statement. The NHMRC CEO agreed to release the CEO Statement for targeted consultation on 13 March 2022.

Following consultation, NHMRC incorporated feedback which was reviewed by the Committee. The CEO Statement underwent expert independent expert review between 14 April and 13 May 2022.

The Council of NHMRC advised the CEO to issue the CEO Statement on 6 June 2022. The CEO agreed to issue the CEO Statement, plain English summary, infographics and supporting

documentation under Section 7(1)(a) of the *National Health and Medical Research Council Act* (1992) (the Act).

Electronic Cigarettes Working Committee

The Electronic Cigarettes Working Committee (the Committee) was established from 5 June 2020 to 4 September 2022 and reported to the Council of NHMRC. Members were found through recommendations from Australian Government Department of Health, people previously known to NHMRC with the required expertise, and a general search conducted by NHMRC. Recommended candidates were approved by the NHMRC General Manager. Committee Members submitted declarations of interest and signed confidentiality agreements.

Appointments to the Committee were made with consideration of expertise required, including research skills, epidemiology, marketing, toxicology and smoking cessation knowledge. Other considerations included expertise in Aboriginal and Torres Strait Islander health, consumer representation, jurisdictional distribution, gender balance and panel size.

Terms of Reference

The Committee Terms of Reference were derived from NHMRC's Memorandum of Understanding with the Australian Government Department of Health, signed prior to the beginning of the project.

In undertaking the update, the Committee will:

1. Determine the scope of the update based on consideration of the currency, accuracy and relevance of the 2017 CEO Statement and other topics such as:
    1. the direct health risks that e-cigarette products (including devices and liquids) may pose to users and non-users (with and without nicotine)
    2. the impact of e-cigarettes on smoking cessation
    3. the impact of e-cigarettes on smoking initiation and continuation
    4. dual use of e-cigarettes and conventional tobacco products
    5. product safety
    6. e-cigarette related advertising and promotional activities and measures
    7. conflicts of interest that may bias research findings related to e-cigarettes
    8. key gaps in the evidence.
2. Guide the development of an evaluation of the evidence, including providing advice on the research protocol/ questions, e-cigarette marketing and use and health outcomes of interest. This includes considering feedback received from methodological review of the draft research protocol and draft evidence evaluation report.
3. Consider the outcomes of the evidence evaluation, and use these findings, in addition to other information as advised by NHMRC, to inform the development of an:

- evidence evaluation report that synthesises the evidence and identifies critical gaps in the current evidence base and
- updated CEO Statement.

4. Consider feedback received during targeted consultation and independent expert review on the draft CEO Statement.

Membership

- Professor Catherine Chamberlain (Chair), Professor of Indigenous Health, Melbourne School of Population and Global Health.
- Professor Matthew Peters (Deputy Chair), Respiratory Physician and Head of Respiratory Medicine at Concord Hospital.
- Professor Renee Bittoun, Professor of Medicine at the University of Notre Dame Australia
- Associate Professor Richard Brightwell, Health Consumers Council, Western Australia.
- Professor Dallas English, Chair of Epidemiology & Biostatistics, and Director of Medicine, Dentistry and Health Sciences at the University of Melbourne.
- Associate Professor Becky Freeman, Associate Professor and Senior Lecturer at the School of Public Health at the University of Sydney.
- Dr Kerry Nugent, Principal Scientist at the Australian Industrial Chemicals Introduction Scheme (AICIS).
- Professor Margaret Otlowski, Professor in the Faculty of Law at the University of Tasmania.
- Professor David Thomas, Professor of Wellbeing and Preventable Chronic Diseases Division, Menzies School of Health Research.
- Professor Nick Zwar, Executive Dean, Faculty of Health Sciences at Bond University.

Observer

- William Parry, Australian Government Department of Health.

Meetings

The Committee met six times via videoconference between 2020 and 2022 to develop research protocols, consider the evidence, and provide review of the draft CEO Statement.

Declaration of interests

Committee members were required to declare their interests in writing prior to appointment, in accordance with NHMRC's *Policy on the Disclosure of Interests Requirements for Prospective and Appointed NHMRC Committee Members*. Throughout the project and at each Committee meeting, members were reminded of their obligation to consider any interest that may have risen since the last meeting or with any agenda items. A record of interests was managed by NHMRC. Following review by NHMRC, no interests were identified that were deemed to require management or rendered members unable to participate in Committee functions.

Electronic Cigarettes Toxicology Subcommittee

The Electronic Cigarettes Toxicology Subcommittee (Subcommittee) was formed to advise on the development of the *Inhalation toxicity of non-nicotine e-cigarette constituents: risk assessments, scoping review and evidence map report (toxicology report)*. Electronic Cigarettes Working Committee members put forward their interest in sitting on the Subcommittee. The observer was recommended by the Electronic Cigarettes Working Committee's toxicologist Dr Nugent, who put forward Dr Schyvens due to his extensive expertise in this area. The Subcommittee met once in 2021 to advise on the scope of work.

Membership

- Professor Catherine Chamberlain, Professor of Indigenous Health, Melbourne School of Population and Global Health.
- Professor Renee Bittoun, Professor of Medicine at the University of Notre Dame Australia.
- Dr Kerry Nugent, Principal Scientist at the Australian Industrial Chemicals Introduction Scheme (AICIS).

Observer

- Dr Chris Schyvens, Director of Toxicology Section at the Therapeutic Goods Administration.

Declaration of interests

Members of the Subcommittee were required to declare their interests in accordance with NHMRC's *Policy on the Disclosure of Interests Requirements for Prospective and Appointed NHMRC Committee Members*. Throughout the project and at each Committee meeting, members were reminded of their obligation to consider any interest that may have risen since the last meeting or with any particular agenda items. A record of interests was managed by NHMRC. Following review by NHMRC, no interests were identified that were deemed to require management or rendered members unable to participate in Subcommittee functions.

Statement Development

Scoping

NHMRC undertook a scoping activity to help the Committee to determine the scope of the CEO Statement, including priority topics and formation of research questions.

At the time of scoping, there was increasing concern about the use of e-cigarettes that are sold as not containing nicotine. Health authorities were unsure as to the health effects of these products, even though they are promoted by the tobacco industry as not containing (harmful)

nicotine. NHMRC conducted a scoping review of the evidence on the health effects of exposure to non-nicotine e-cigarettes. The search was conducted via two strategies to determine recent information on non-nicotine e-cigarettes:

1. literature review of articles published since 2014
2. review of grey literature, specifically, research reports published since 2014 commissioned by the Australian Government.

The search was completed through the PubMed database on 14 November 2019. A supplementary grey literature search was also conducted on the following websites: World Health Organization (WHO), Australian Institute of Health & Welfare (AIHW), australia.gov.au and google.com.au for recent government reports published since 2014. Recent reports published by the United States Centers for Disease Control and Prevention were also included.

The scoping activity concluded that a large majority of the evidence did not differentiate between nicotine-containing and non-nicotine containing e-cigarettes. In consultation with the Committee, it was agreed for the project scope to be broadened to include nicotine-containing e-cigarettes. It was noted that where possible, that the evidence for nicotine-containing products was distinguished from non-nicotine products.

Evidence

A range of inputs was considered in revising the CEO Statement, that included:

- commissioned evidence reviews
- toxicological information
- evidence and position statements from other countries
- the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) 2018 evidence statements and report
- the Commonwealth Scientific Investigation and Research Organisations (CSIRO) Review
- relevant reports from the United States Surgeon General
- data on e-cigarette usage, sociodemographic and other features of the Australian community
- the shared expertise of the Electronic Cigarettes Working Committee
- feedback from targeted consultation with federal, state and territory Chief Health/ Medical Officers
- feedback from independent exert reviewers
- NHMRC and international best practice guidance for development of guidelines and health guidance.

Evidence reviews

Several evidence reviews were commissioned by both the Australian Government Department of Health and NHMRC to underpin the CEO Statement. The evidence reviews were commissioned as follows:

Australian Government Department of Health

The National Centre for Epidemiology and Population Health (NCEPH)

To provide a comprehensive analysis of current e-cigarette use in the Australian context, the Australian Government Department of Health commissioned the National Centre for Epidemiology and Population Health (NCEPH) to conduct the following evidence reviews:

- *E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis*
- *Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review*
- *Electronic cigarettes and health outcomes: systematic review of the global evidence.*

To alleviate crossover of research activities between the commissioned projects, NHMRC used the evidence reviews produced by NCEPH to form part of the evidence for the update of the CEO Statement.

NHMRC

As part of the CEO Statement update, NHMRC commissioned evidence reviews from:

The George Institute for Global Health (TGI)

- *Effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs, perception, intentions, and behaviours: a mixed-methods systematic review*

National Centre for Epidemiology and Population Health (NCEPH)

- *Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*
- *Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure.*

The independent evaluations of the evidence were undertaken in accordance with research protocols approved by the NHMRC Project Team, based on advice from the Committee. For each review, the research protocols outlined the scope, research question and methodology. The finalised evidence reviews, technical reports and supplementary reports were published on the NHMRC website in June 2022, to coincide with the release of the revised CEO Statement.

NHMRC Toxicology Report

At the second meeting of the Committee, NCEPH noted that toxicology of e-cigarettes was largely beyond the scope of their health outcomes review and the expertise of their team. The Committee advised that a review of the evidence on the toxicology of non-nicotine e-cigarette constituents was required to inform the CEO Statement and should be included in addition to

the original scope of evidence on e-cigarette use, marketing and health for the review. A Subcommittee was established to oversee this branch of the work. The Subcommittee agreed that NHMRC would develop a report on the toxicology of e-cigarettes.

The NHMRC project team developed a project proposal. The NHMRC Senior Principal Research Scientist advised that the project scope was too large and the research question too broad to do a systematic review within the given timeframes. The NHMRC project team consulted the toxicologists on the Subcommittee, Dr Nugent and Dr Schyvens, to discuss the complexities and limitations of the proposed approach given the timeframes, and to refine the project scope. The project scope was refined to identifying the available evidence in the form of a scoping review of the scientific literature and an analysis of published toxicological assessment data. Given the limitations of the study design of the toxicology report, it was agreed that the report would be used to provide contextual information in the development of the CEO Statement.

The revised project proposal was reviewed and endorsed by the Subcommittee. A research protocol was developed for the scoping review component of the toxicology report and was reviewed by the Subcommittee and NHMRC Senior Principal Research Scientist. As recommended by the Subcommittee, an information scientist from the Information Resources and Research Services Library revised the search string and suggested edits to ensure search results were relevant to the research question. The protocol was independently methodologically reviewed by Cochrane Australia, with feedback incorporated into the final version. The protocol was published online on Figshare.

The toxicology report was developed by the NHMRC project team with input and review by the Subcommittee. The scoping review component of the toxicology report was independently methodologically reviewed by Cochrane Australia to ensure it followed the research protocol. Feedback from the methodological reviewers, Subcommittee and Committee was incorporated into the final version. The final toxicology report was endorsed by the Committee in February 2022.

Independent methodological review of evidence

The evidence reviews, supporting materials and supplementary reports produced by NCEPH and TGI were independently methodologically reviewed by HealthConsult. HealthConsult examined the methodological quality of the evidence review reports to ensure that the reviews followed the systematic and rigorous approach documented in the review protocols. Feedback provided by HealthConsult was considered by NHMRC and the Committee prior to the finalisation of the evidence reviews.

Section 4.3 dependency and abuse liability of the *Electronic cigarettes and health outcomes: systematic review of the global evidence*, was updated after the methodological review was conducted by HealthConsult. Professor Dallas English, a member of the Electronic Cigarettes Working Committee, conducted an additional methodological review of the updated section. Feedback provided was considered by NHMRC and the Committee prior to the finalisation of the evidence review.

As previously mentioned, the scoping review component of the NHMRC toxicology report was methodologically reviewed by Cochrane Australia to ensure if followed the systematic approach detailed in the review protocol.

Evidence to translation

The evidence was synthesised and translated into the CEO Statement in three phases:

1. Certainty of evidence

As per the NHMRC *Guidelines for Guidelines Handbook*, GRADE[1] was used to assess the certainty of evidence. Committee members reviewed the GRADE assessments for the following evidence reviews and their associated reports:

- *Effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs, perception, intentions, and behaviours: a mixed-methods systematic review*
- *E-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers: umbrella review, systematic review and meta-analysis*
- *Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review*
- *Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation*
- *Electronic cigarettes and health outcomes: systematic review of the global evidence*
- *Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure*

A Delphi-survey approach was used to consolidate member assessments. Members were asked to agree or disagree with the provided assessment and provide a rationale for their response, including an alternate GRADE assessment, where applicable. When a GRADE assessment was not provided in the evidence review NHMRC conducted a GRADE assessment for inclusion in the Delphi survey (for example, for secondary outcomes or if a different quality assessment tool was used such as the Newcastle-Ottawa scale). NHMRC GRADE assessments can be found at Appendix A.

Prior to beginning the Delphi surveys, Committee members agreed that bodies of evidence that consist of:

- RCTs will assume an initial level of certainty of "high"
- Prospective cohort studies will assume an initial level of certainty of "moderate"
- All other observational studies will assume an initial level of certainty of "low".

The survey results were collated by NHMRC into a technical report. A summary of the survey results was incorporated into an evidence-to-decision matrix (Appendix B) and this matrix was discussed by Committee members. Committee members endorsed the technical report to form the basis for writing the evidence statements (Appendix C). Committee members reviewed and finalised the evidence statements out-of-session.

[1] Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from guidelinedevelopment.org/handbook.

In conjunction with advice from the NHMRC Senior Principal Research Scientist, the Committee members agreed that due to the nature of the toxicology report (scoping review) that it was not appropriate to assess certainty of evidence or draw conclusions from this report. The toxicology report was used to provide contextual information in the development of the CEO Statement.

2. Evidence-to-decision framework

The WHO-INTEGRATE evidence-to-decision framework[2] was used to develop the updated CEO Statement. The WHO-INTEGRATE evidence-to-decision framework has been designed for decision-making at population levels and was considered well-suited to the development of public health advice, such as the updated CEO Statement.

Typically, the WHO-INTEGRATE framework is used to assess public health recommendations against as set of criteria. As the CEO Statement does not include recommendations, the framework was adapted to shape and write the CEO Statement, for example which evidence to include and emphasise, and the wording of key messages.

The WHO-INTEGRATE framework was discussed by the Committee at Committee Meeting 5. Outcomes of the discussion were summarised in the evidence-to-decision matrix (Appendix B).

3. Evidence statements

The Santesso et al (2020) *Informative statements to communicate the findings of systematic reviews of interventions*[3] was used to inform the terminology of the evidence statements (Appendix C). The certainty of evidence was determined based on the results from the series of Delphi surveys undertaken by Committee members. Magnitude/size of effect was based on data presented in the evidence reviews. Where no measures of effect were available, a generalised, narrative summary was used that described the direction of effect (that is, increase/reduction) but not the size of the effect (that is, slight/large or increase/reduction).

Definitions of large, moderate, small important, trivial/small unimportant were based on the GRADE approach[4] and Sullivan and Feinn (2012)[5]. A summary of the definitions can be found below:

Magnitude of effect	Measure of effect	Other considerations
Large	Relative risk or risk ratio (RR): ≥4.0 Odds ratio (OR): ≥3.0	Based on direct evidence, no plausible confounders and no serious problems with risk of bias or precision.

[2] Rehfuess EA, Stratil JM, Scheel IB, et al. The WHOINTEGRATE evidence to decision framework version
1.0: integrating WHO norms and values and a complexity perspective. BMJ Glob Health 2019;4:e000844. doi:10.1136/bmjgh-2018-000844
[3] Santesso N et al.; GRADE Working Group. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. J Clin Epidemiol. 2020 Mar;119:126-135. doi: 10.1016/j.jclinepi.2019.10.014. Epub 2019 Nov 9. PMID: 31711912.
[4] GRADE Working Group (2013). GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. H. Schünemann, J. Brożek, G. Guyatt and A. Oxman.
[5] Sullivan GM, Feinn R. Using Effect Size-or Why the P Value Is Not Enough. J Grad Med Educ. 2012;4(3):279-282. doi:10.4300/JGME-D-12-00156.1

Magnitude of effect	Measure of effect	Other considerations
		Downgrade if confounders are present or not managed, and/or there are serious problems with risk of bias or precision.
Moderate	RR: 3.0 OR: 2.0	Downgrade if confounders are present or not managed, and/or there are serious problems with risk of bias or precision.
Small, important	RR: 2.0 OR: 1.5	Downgrade if confounders are present or not managed, and/or there are serious problems with risk of bias or precision.
Trivial/small, unimportant	RR: <2.0 OR: <1.5	Confounders are present or not managed, and/or there are serious problems with risk of bias or precision.

Evidence statements for single studies

Evidence statements were generated for high-quality single studies, which were defined as being of moderate or high certainty of evidence. Evidence statements for single studies included the following preface “evidence from a single study suggests…”.

Draft CEO Statement

The CEO Statement provides public health advice on the safety and impacts of electronic cigarettes (e-cigarettes) based on review of the current evidence. Technical writing was executed by the NHMRC project team in consultation with the Committee. The evidence-to-decision matrix and evidence statements were used to inform the update to the 2017 CEO Statement. A Committee meeting was held to discuss initial Committee feedback and obtain consensus on any conflicting feedback. The Committee reviewed and endorsed a final draft of the CEO Statement out-of-session to send out for targeted consultation.

Targeted consultation

As per the Memorandum of Understanding between NHMRC and the Australian Government Department of Health, the draft CEO Statement was circulated to federal, state and territory Chief Health Officers/Chief Medical Officers for targeted consultation over a two-week period in March 2022. Chief Health Officers/Chief Medical Officers were also asked to contribute Poisons Information Centre data on nicotine poisoning for inclusion in the CEO Statement (if available) and to comment on two infographic concepts that summarised the CEO Statement.

Overall, Chief Health Officers/Chief Medical Officers were supportive of the CEO Statement. In response to feedback, edits to the CEO Statement were made, including the addition of a plain English summary of the CEO Statement. Any feedback received from jurisdictional Chief Health Officers during the independent expert review period was addressed, where appropriate, in the final version of the CEO Statement.

Independent expert review

The NHMRC 2016 Standards for Guideline Development recommend appropriate peer review of draft guidelines or health advice. The Electronic Cigarettes Working Committee

(Committee) and the Department of Health suggested several reviewers. Acceptance criteria for individuals who could undertake expert review of draft CEO Statement included:

- having appropriate knowledge of the evidence base on e-cigarettes
- strong research methodology and/or epidemiology skills
- having familiarity or experience with the translation of public health evidence into advice or guidelines (including assessing certainty of evidence) being highly desirable
- declaring interests according to NHMRC policies, and any interests being deemed either not in conflict with the guideline development process, or manageable through an appropriate strategy.

Independent expert review of the CEO Statement was undertaken between 14 April and 6 May 2022. The following expert reviewers provided their comments on the draft CEO Statement to ensure that the evidence on e-cigarettes had been appropriately interpreted and synthesised in the CEO Statement:

- Professor Richard Edwards
- Associate Professor Coral Gartner
- Associate Professor Alexander Larcombe

Professor Melanie Wakefield and Dr Michelle Scollo agreed to conduct a joint review. They had to withdraw due other commitments.

Expert reviewers were asked to consider:

- Is the CEO Statement appropriate in its readability and usefulness, given the target audience?
- Has the appropriate evidence been identified and reviewed? Has any evidence been missed, given the scope of the update?
- Has the body of evidence been appropriately considered and translated in line with the WHO-INTEGRATE evidence-to-decision framework?
- Have the issues raised during targeted consultation been appropriately addressed?
- Are there other high quality international public health statements of advice or guidelines on e-cigarettes and how does their advice and/or recommendations align with the CEO Statement?

Overall, the reviewers considered that the evidence on e-cigarettes had been appropriately interpreted and synthesised in the CEO Statement, with some minor edits for clarity recommended. Reviewers noted the challenge in simplifying the complexities of the evidence base into accessible language. Minor suggestions were incorporated into the final CEO Statement and plain-English summary, as appropriate and guided by advice from the Electronic Cigarettes Working Committee.

It was raised that evidence of high certainty and low incidence as presented in the plain-English summary could be misinterpreted. NHMRC worked with the Committee to develop an approach which balanced simplifying the evidence statements, whilst minimising the potential for the evidence to be misinterpreted. This approach was used in the final version of the plain-English summary.

Some of the feedback received from expert reviewers was beyond the scope of the expert review process, for example, anecdotal commentary on the evidence or inclusion of evidence statements from studies outside those examined by the Committee. These types of suggestions were not incorporated, as they did not reflect the evidence and data examined. During the development of the CEO Statement, the Committee acknowledged that the

evidence base on e-cigarettes is rapidly evolving and that there is a diverse range of opinions and guidance provided on e-cigarettes. This has been acknowledged in the CEO Statement.

Council Approval

The CEO Statement was considered by Council of NHMRC out of session on 6 June 2022. Council advised the CEO to issue the CEO Statement. The NHMRC CEO agreed to issue the CEO Statement under Section 7(1a) of the NHMRC Act.

Appendix A: NHMRC GRADE assessment

The umbrella review, systematic review and meta-analysis examining e-cigarette use and combustible tobacco cigarette smoking uptake among non-smokers, including relapse in former smokers, used the Newcastle-Ottawa scale and AMSTAR 2 to assess quality. The table below is a summary of GRADE assessments[6] conducted by NHMRC for these outcomes.

Outcome	Population group	Exposure type	Comparator	Measure of effect (eg, OR/RR)	95% CI/p-value	Study type (reference(s))	No. participants	Certainty of evidence	Rationale
Smoking initiation	Never smokers	Users of e-cigarettes	Non-users of e-cigarettes	OR 3.19	95% CI: 2.44 – 4.16	Cohort (Berry 2019; Chien 2019; McMillen 2019; Primack 2018; Loukas 2018; East 2018; Best 2018; Treur 2018; Barrington-Trimis 2018; Lozano 2017; Miech 2017; Spindle 2017; Wills 2017; Leventhal 2015; Primack 2015) RCTs (Conner 2019; Penzes 2018)	Not specified	Low	**Risk of Bias: not serious; Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2=87.07%.; **Publication bias: serious.** Asymmetrical funnel plot; sensitivity analyses conducted in Supplementary Report 1 did not identify commercially-funded studies; result remain unchanged.
Current (past 30 day) smoking	Non-current smokers	Current e-cigarette users	Non-current e-cigarette users	OR 3.14	95% CI: 1.93 – 5.11	Cohort (Osibogun 2020; Aleyan 2019; Barrington-Trimis 2019; Conner 2019; Kinnunen 2019; McMillen 2019; Bold 2018; Unger 2016)	Not specified	Very low	**Risk of Bias: serious.** due to confounding and participant selection; **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, with I^2=90.95%.; **Indirectness: not serious.** Most studies have been conducted in the USA and none in Australia. Differences in legislation, taxation, social norms and public opinion may cause confounding ; **Publication bias: serious.** Asymmetrical funnel plot; sensitivity analyses conducted in Supplementary Report 1 did not identify commercially-funded studies; result remain unchanged.
Smoking relapse	Former smokers	Current e-cigarette users	Never e-cigarette users	OR 2.40	95% CI: 1.50 – 3.83	Cohort (Brose 2019; Dai 2019; McMillen 2019)	Not specified	Low	**Risk of Bias: serious.** due to confounding and participant selection; **Inconsistency: not serious.** Low heterogeneity I^2=12.31%.

The mixed-methods systematic review on the effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs, perceptions, intentions, and behaviours did not provide GRADE assessments for secondary outcomes. The table below is a summary of GRADE assessments conducted by NHMRC for these outcomes.

[6] Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available

Outcome	Population group	Exposure type* *e-cigarette advertising unless otherwise specified	Comparator	Measure of effect (eg, OR/RR)	95% CI/p-value	Study type (reference(s))	No. participants	Certainty of evidence	Rationale
Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Billboard/poster advertising - exposure	Billboard/poster advertising – no exposure	OR: 1.22	95% CI: 0.87 – 1.72	Cohort (Chen-Sankey 2019; Nicksic 2017a)	13,711	Very low	**Risk of Bias: serious.** Nicksic 2017 is a recall study and it was unclear if follow up was complete and whether strategies to address incomplete follow up were used; both studies had relatively short follow-up periods (6 months & 1 month); **Inconsistency: not serious.** Low heterogeneity (I^2=0%); **Indirectness: very serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; Populations differ between the two studies - one looks at never smokers (e-cigs and traditional cigs), the other looks at never, ever and current users of e-cigs; **Imprecision: serious.** Confidence interval includes the line of no effect (that is, CI includes 1.0); **Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Adolescents	Internet advertising - exposure	Internet advertising – no exposure	OR: 1.80	95% CI: 1.28 – 2.54	Cross-sectional (Mantey 2016; Pu 2017; Unger 2018)	57,253	Very low	**Risk of Bias: not serious.** Unclear for one study whether confounding factors were identified, that said, appropriate measures were put in place to manage confounding. For another study confounding factors were not identified and unclear if controlled for in analysis. **Inconsistency: serious.** High heterogeneity (I^2=90%). **Indirectness: very serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding. One study specifically assessed exposure via tobacco brands' Internet websites compared to general internet websites being assessed in the other two studies. **Imprecision: not serious. Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	OR: 1.28	95% CI: 1.04 – 1.58	Cohort (Chen Shanky 2019; Nicksic 2017a)	12,292	Very low	**Risk of Bias: serious.** Nicksic 2017 is a recall study and it was unclear if follow up was complete and whether strategies to address incomplete follow up were used; both studies had relatively short follow-up periods (6 months & 1 month); **Inconsistency: not serious.** Low/moderate heterogeneity (I^2=35%); **Indirectness: very serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; Populations differ between the two studies - one looks at never smokers (e-cigs and traditional cigs), the other looks at never, ever and current users of e-cigs; **Imprecision: serious.** Confidence interval includes the line of no effect (that is, CI includes 1.0); **Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Adolescents and young adults	Multiple media sources – exposure	Multiple media sources – no exposure	OR: 1.11	95% CI: 1.08 – 1.14	Cross-sectional (Mantey 2016; Pokhrel 2017)	22,477	Very low	**Risk of Bias: serious.** Pokhrel (2015) unclear whether the survey instruments used to measure exposure and outcome were valid and reliable. For Mantey 2016 it was unclear whether confounding factors were identified; **Inconsistency: serious.** No heterogeneity (I^2=0%); the direction of the effect is not consistent between the included studies; **Indirectness: serious.** The studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; **Imprecision: Not serious.**

Outcome	Population group	Exposure type* *e-cigarette advertising unless otherwise specified	Comparator	Measure of effect (eg, OR/RR)	95% CI/p-value	Study type (reference(s))	No. participants	Certainty of evidence	Rationale
Intentions to use e-cigarettes	Adolescents	Print media advertising - exposure	Print media advertising – no exposure	OR: 1.24	95% CI: 1.13 – 1.35	Cross-sectional (Mantey 2016, Pu 2017)	43,602	Very low	**Risk of Bias: not serious.** For Mantey 2016 it was unclear whether confounding factors were identified, that said, appropriate measures were put in place to manage confounding. Adjusted for gender, race/ethnicity, grade, and other tobacco use (cigarettes, cigars, hookah, smokeless, snus, pipes, bidis, dissolvable). **Inconsistency: not serious.** I^2=0%; **Indirectness: serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; **Imprecision: not serious. Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Radio advertising - exposure	Radio advertising – no exposure	OR: 1.36	95% CI: 0.92 – 2.01	Cohort (Chen-Sankey 2019; Nicksic 2017a)	13,711	Very low	**Risk of Bias: serious.** Nicksic 2017 is a recall study and it was unclear if follow up was complete and whether strategies to address incomplete follow up were used; both studies had relatively short follow-up periods (6 months & 1 month); **Inconsistency: not serious.** Low heterogeneity (I^2=0%); **Indirectness: very serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; Populations differ between the two studies - one looks at never smokers (e-cigs and traditional cigs), the other looks at never, ever and current users of e-cigs; **Imprecision: serious.** Confidence interval includes the line of no effect (that is, CI includes 1.0); **Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Television advertising - exposure	Television advertising – no exposure	OR: 1.41	95% CI: 1.02 – 1.94	Cohort (Chen-Sankey 2019; Nicksic 2017a)	13,711	Very low	**Risk of Bias: serious.** Nicksic 2017 is a recall study and it was unclear if follow up was complete and whether strategies to address incomplete follow up were used; both studies had relatively short follow-up periods (6 months & 1 month); **Inconsistency: not serious.** Low heterogeneity (I^2=0%); **Indirectness: very serious.** Studies were conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding; Populations differ between the two studies - one looks at never smokers (e-cigs and traditional cigs), the other looks at never, ever and current users of e-cigs; **Imprecision: not serious. Publication bias: not serious.** No interests to declare.
Intentions to use e-cigarettes	Young adults – Never e-cigs users and less than 100 cigarettes smoked in lifetime	Multiple media advertising - Exposure to ads that promoted e-cigs as cessation aids	Multiple media advertising – exposure to Control advertisements (of everyday items; ie, did not promote e-cigs)	Standardised regression coefficients 0.05	SE 0.02 p = 0.04	Randomised controlled trial (Pokhrel 2019)	393	Moderate	**Risk of Bias: serious.** Only mentioned that participants were randomly assigned but no other information on method of sequence generation was reported; Insufficient reporting of attrition, withdrawals and blinding. **Inconsistency: not serious; Indirectness: serious.** This study was conducted in USA. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding. **Imprecision: serious.** Only one study; p value statistically significant; **Publication bias: not serious.**

Outcome	Population group	Exposure type* *e-cigarette advertising unless otherwise specified	Comparator	Measure of effect (eg, OR/RR)	95% CI/p-value	Study type (reference(s))	No. participants	Certainty of evidence	Rationale
Current e-cigarette use	Adolescents and young adults	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	OR: 1.30	95% CI: 1.13 – 1.50	Cross-sectional Studies (Auf 2018, Cho 2019, Hansen 2018, Papaleontiou 2020, Donaldson 2017, Filippidis 2017)	27,801	Very low	**Risk of Bias: not serious.** For Papaleontiou 2020 confounders were not identified but covariates were adjusted in statistical analysis. It was unclear whether the outcomes measurements were valid and reliable for Donaldson 2017. **Inconsistency: serious.** The magnitude of statistical heterogeneity was moderate/high, with I^2=70%. **Indirectness: Serious.** Studies were conducted in USA, Canada, UK and Europe. Differences in advertising legislation, taxation, social norms and public opinion may cause confounding. **Imprecision: Not serious. Publication Bias: Not serious.** Demonstrate demonstrating dose response in Auf 2018, Cho 2019, Hansen 2018, Papaleontiou 2020 when pooled together.

Appendix B: Evidence-to-decision matrix

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Balance of health benefits and harms				
Non-smokers	8 of 8 members agreed that the harms/burdens of e-cigarette use by non-smokers clearly outweigh the benefits.	Members briefly discussed use of nicotine as a performance enhancer. Consensus that the harms/burdens of using e-cigarettes clearly outweigh the benefits for non-smokers.	One report noted the use of e-cigarettes results in inhalation of a complex array of chemicals originating from the e-liquid, chemical reactions in the heating coil and the device itself. These include nicotine, solvent carriers (propylene glycol, ethylene glycol and glycerol), tobacco-specific nitrosamines, volatile organic compounds, phenolic compounds, flavourings, tobacco alkaloids, aldehydes, free radicals, reactive oxygen species, furans and metals. Toxicological studies indicate that exposure to these substances can result in adverse health effects. (1). According to the Australian Federal Government, Australia's successful approach to tobacco control over many decades has seen substantial declines in tobacco use among young Australians (2). Between 2002 and 2017, the proportion of secondary school students who were current smokers declined significantly. While 9% of secondary school students were smoking in 2002, in 2017 this had decreased 4-fold to 2% (3). E-cigarettes expose a new generation of young Australians to a risk to their current and future health. (2) One report noted 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. (4) The Australian Government Department of Health noted that research shows a strong association between the use of e-cigarettes by non-smoking youth and future smoking. (5) The NASEM report noted that there is conclusive evidence that in addition to nicotine, most e-cigarette products contain and emit numerous potentially toxic substances. It also noted that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults. Additionally, it stated that some e-liquid cartridges contain nicotine doses that are potentially toxic in adults and children if used in ways other than intended. Intentional or accidental exposure to e-liquids can cause adverse health effects such as seizures, anoxic brain injury, vomiting, lactic acidosis, and death. (6) Is it appropriate to assume that smoking e-cigarettes is more detrimental to human health than never-smoking?	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 2. Australian Department of Health. Policy and regulatory approach to electronic cigarettes (e-cigarettes) in Australia. 2019., https://www.health.gov.au/resources/publications/policy-and-regulatory-approach-to-electronic-cigarettes-e-cigarettes-in-australia. Accessed 30 November 2021. 3. Australian Federal Government. Australian Institute of Health and Welfare: Australia's Children. 2020. https://www.aihw.gov.au/getmedia/6af928d6-692e-4449-b915-cf2ca946982f/aihw-cws-69-print-report.pdf.aspx?inline=true. Accessed 2 December 2021. 4. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 5. Department of Health. About e-cigarettes. 2021., https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/about-e-cigarettes. Accessed 3 December 2021. 6. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	5 of 8 members agreed that the benefits of e-cigarette use by smokers slightly outweigh the harms/burdens.	Members noted that the results are determined based on an assumption that smokers wouldn't have otherwise quit. Similarly, members discussed the importance of distinguishing between e-cigarettes as a consumer product and e-cigarettes for smoking cessation and the importance of looking at the two separate questions.	One report noted that based on random-effects meta-analyses of the current limited evidence, no significant benefit for smoking cessation of freebase electronic nicotine delivery systems (ENDS) versus electronic non-nicotine delivery systems (ENNDS) or approved nicotine replacement therapy (NRT) was detected. (1) The paper also noted there is limited evidence that, in the clinical context in combination with best-practice counselling and supportive care, 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. (1) One report noted that when e-cigarettes are used by smokers instead of conventional cigarettes there is evidence for improvement in individual health. (2) One reported noted the use of e-cigarettes results in inhalation of a complex array of chemicals originating from the e-liquid, chemical reactions in the heating coil and the device itself. (3) A Supplementary Report noted that there is conclusive evidence that e-cigarettes and their constituents cause poisoning, injuries and burns and immediate toxicity through inhalation, including seizures, and that their use leads to addiction and that they cause less serious adverse events, such as throat irritation and nausea. (4) One paper noted are a growing number of varieties of e-cigarettes and solutions, with evidence of large variability between the labelled content and the actual content and concentrations. Differences in battery voltage and unit circuitry can create significant variances in the products' ability to aerosolise the solution, and consequently the amount of nicotine and other constituents delivered to the user (5). Users can also modify many of the products, allowing them to alter delivery of nicotine and/or other drugs.(6) The Australian Government Department of Health stated that many e-cigarette users appear to be continuing to use conventional tobacco products at the same time (dual users). Dual users may be exposing themselves to even higher levels of toxicants compared to people who solely use conventional tobacco products. (7) The NASEM report noted that (i) there is conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes (ii) there is substantial evidence that except for nicotine, under typical conditions of use, exposure to potentially toxic substances from e-cigarettes is significantly lower compared with combustible tobacco cigarettes (iii) there is substantial evidence that nicotine intake from e-cigarette devices among experienced adult e-cigarette users can be comparable to that from combustible tobacco cigarettes (iv) there is substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems (8)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021. 3. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 4. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 5. Cheng T. Chemical evaluation of electronic cigarettes. *Tobacco Control*. 2014; 23:ii11-ii17. 6. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control. 2016. 7. Department of Health. About e-cigarettes. 2021., https://www.health.gov.au/health-topics/smoking-and-tobacco/about-smoking-and-tobacco/about-e-cigarettes. Accessed 3 December 2021. 8. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Human rights and socio-cultural acceptability				
Non-smokers	6 of 8 members agreed that acceptability of e-cigarettes by non-smokers varies.	Members discussed: - rapidly changing social norms and the difficulty in capturing this information; - product acceptability and portrayal in marketing; - difficulty of consenting to a product where there are still unknowns; - issues with product labelling (for example, those that do not state nicotine content) and the ability of individuals, especially young and vulnerable populations to provide consent.	One report noted that a summary of 6 studies looking at perceptions of risk noted that participants, particularly adolescents and young adults, reported e-cigarette advertisements often claimed the products were healthier than combustible cigarettes. Many stated that exposure to such advertisements made them believe e-cigarettes were either less dangerous than cigarettes or not harmful at all. (1) It also noted that in a summary of 3 studies looking at exposure to 'vape tricks' on social media found that Participants who reported having seen social media videos that included tricks or tutorials believed that using e-cigarettes was 'trendy,' 'cool', and 'fun'. Additionally, participants who reported viewing social media videos appeared to have greater interest in e-cigarettes. (1) It has been noted that among adolescents, e-cigarettes are generally perceived as less harmful than conventional cigarettes, and also as less addictive. (2)(3)(4)	1. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 2. Greenhalgh EM, Scollo MM and Winstanley MH. Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021. 3. East K, Brose LS, McNeill A, et al. Harm perceptions of electronic cigarettes and nicotine: A nationally representative cross-sectional survey of young people in Great Britain. *Drug and Alcohol Dependence*. 2018; 192:257-63. 4. Cooper M, Harrell MB, Perez A, et al. Flavourings and perceived harm and addictiveness of e-cigarettes among youth. *Tobacco Regulatory Science*. 2016; 2(3):278-89.
Smokers	5 of 8 members agreed that acceptability of e-cigarettes by smokers varies.	Members discussed: - concerns regarding re-addiction when shifting to e-cigarettes; - the product [e-cigarettes] is acceptable but it is addictive which has an impact on human rights (it is a human right to be able to stop/quit something/not become addicted); - availability of other NRTs. Members noted that e-cigarettes are likely to be less acceptable to non-smokers and more acceptable to smokers.	One study on perceptions and beliefs found that e-cigarettes are often perceived as being cheaper than smoking regular cigarettes. (1) A US report found that heightened focus on the effects of certain policies is needed because of their potential impacts on public health. These include policies applying to the use of cigarettes and noncigarette tobacco products and strategies addressing populations that have limited access to cessation interventions (for example, the rural poor, psychiatric populations, low-income and unemployed persons, homeless populations, and individuals who are incarcerated). (2) Two studies noted that although initially slow to enter the market, the major international tobacco companies have invested heavily in e-cigarettes in recent years, and tobacco companies now own many of the top e-cigarette brands. (3)(4). Is it appropriate to assume that they profit off the use and sale of e-cigarettes and they would decrease profits if e-cigarettes were to be further regulated or banned? Is it appropriate to assume that regulating and banning access to e-cigarettes may encroach on a person's autonomy to do what they want with their body? Cancer Council NSW noted that there are other Nicotine Replacement Therapies on the market to assist with smoking cessation, such as patches, gum, lozenges, mini-lozenges & inhalers. (5)	1. Villanti AC, Rath JM, Williams VF, et al. Impact of exposure to electronic cigarette advertising on susceptibility and trial of electronic cigarettes and cigarettes in US young adults: A randomized controlled trial. *Nicotine Tobacco Research.* 2016; 18(5):1331-9. 2. US Department of Health and Human Services. Smoking Cessation. A Report of the Surgeon General. 2020. https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf. Accessed 29 November 2022. 3. Greenhalgh EM, Scollo MM and Winstanley MH. Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021. 4. Bauld L, Angus K, De Andrade M and Ford A. Electronic Cigarette Marketing: Current Research and Policy. *Cancer Research.* 2016. p72. 5. Cancer Council NSW. NRT Factsheet. 2016. https://www.cancercouncil.com.au/wp-content/uploads/2016/09/16138_CA_CAN5084_NRTFactsheet_WEB.pdf. Accessed 3 December 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Health equity, equality, and non-discrimination				
Non-smokers	4 of 8 members agreed that health equity/equality is reduced for non-smokers. Other responses: 3 of 8 members voted health equity was probably reduced. 1 of 8 members voted that health equity increased.	Members discussed: - e-cigarette use among youth; - price of e-cigarettes and subsequent accessability; - young people are being targetted (product marketing, but also product flavours and labelling); - pattern of dependence in the next generation.	One report stated that risks may also be greater in certain priority populations including Aboriginal and Torres Strait Islander communities and people with mental health problems.(1) One report noted that when regarding attitudes, beliefs and sponsorship, across the examined exposure and outcome types, most studies focused on the population groups of adolescents and/or young adults. Greater attention to differences according to socioeconomic position and other equity indicators would be useful for providing a more detailed understanding of which groups may be most adversely affected by e-cigarette advertising. The majority of the studies controlled for covariates such as age and gender. It is possible that residual factors (for example, greater access to the Internet, social media, or tobacco retail outlets) may have influenced the results in terms of association between exposure and the outcome. (2)	1. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021.
Smokers	5 of 8 members agreed that health equity/equality varies for smokers.	Members discussed: - Benefits to some smokers; - Commercial considerations; - Composite effect is not impacted, positive and negative impact.	One report stated that risks may also be greater in certain priority populations including Aboriginal and Torres Strait Islander communities and people with mental health problems. (1) One book stated that any population-level effects may include some groups incurring harm (for example, young people who start smoking), and some incurring benefits (for example, smokers who quit). (2) Is it appropriate to assume that facilitating smoking cessation in low-socioeconomic status (low-SES) smokers is a national health priority?. Cancer Council NSW noted that there are other Nicotine Replacement Therapies on the market to assist with smoking cessation, such as patches, gum, lozenges, mini-lozenges & inhalers. (3) In considering ENDS as a potential cessation aid, smokers should first be encouraged to quit smoking and nicotine addiction using a combination of already approved treatments. However, at the individual level, experts suggest that in some smokers who have failed treatment, have been intolerant to it or who refuse to use conventional smoking cessation medication, the use of appropriately regulated ENDS may have a role to play in supporting attempts to quit. (4)	1. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Greenhalgh EM, Scollo MM and Winstanley MH. , Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021. 3. Cancer Council NSW. NRT Factsheet. 2016. https://www.cancercouncil.com.au/wp-content/uploads/2016/09/16138_CA_CAN5084_NRTFactsheet_WEB.pdf. Accessed 3 December 2021. 4. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control; 2016.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Societal implications				
Non-smokers	5 out of 8 members agreed that e-cigarettes limits achievement of social/environmental goals.* * with the caveat that carbon neutral vapes do not address this problem.	Member discussed: - How the education system are dealing with e-cigarettes; - Complexities of dependence in children and youth; and - Lack of available public health guideance for schools.	One report noted that studies show that e-cigarettes are marketed on a range of online platforms. Due to the borderless nature of social media, posts from any country can be viewed in Australia on these platforms and, as such, international practices are relevant here. (1) One paper noted that the major global social media platforms have enacted policies regarding tobacco marketing that in most cases extend to e-cigarettes. The policies for the majority of these platforms do not extend to the accounts of individuals, including influencers and fan pages/groups (2) One report stated that use is more common among youth, among males and among smokers and the majority is not for the purposes of smoking cessation; 53% of current e-cigarette use is dual use in people who also smoke, 31.5% is in past smokers and 15.5% is in never-smokers. (3) One report noted that e-cigarette environmental impacts include waste, fires and indoor airborne particulate matter, which, in turn, are likely to have adverse health impacts, the extent of which cannot be determined. (3) One review stated that in respect to the effects of passive smoking secondary to electronic cigarettes use, there exists a complete paucity of evidence regarding the acute and long-term effects of passive smoking secondary to electronic cigarettes on cardiovascular and other health outcomes in children and adolescents. It noted that further research investigations are urgently mandated for evaluating the effects of passive smoking induced by electronic cigarettes use in susceptible populations, particularly such as children and adolescents who may be regularly exposed within their home environments. (4) One report found that while some proponents of e-cigarettes argue they are an effective smoking cessation tool, the benefits remain equivocal and a growing body of research supports the proposition that e-cigarettes can act as a gateway to cigarette smoking, particularly among youth. (1) One report stated that the most common messages in online posts about e-cigarettes were found to be about health, safety, and harms. This content typically referred to e-cigarettes as being less harmful than conventional tobacco products. The second most common messages were those promoting the use of e-cigarettes as a smoking cessation tool, and the third were those emphasising certain product types and characteristics such as brands, flavours, and nicotine content. (1) NASEM reported that: (i) there is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels (ii) there is moderate evidence that secondhand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes. (5)	1. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 2. McCausland K, Maycock B, Leaver T, et al. E-Cigarette promotion on Twitter in Australia: Content analysis of Tweets. JMIR Public Health and Surveillance 2020; 6(4):e15577. 3. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 4. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021. 5. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members responses varied.* 3 of 8 members voted that the use of e-cigarettes in smokers possibly limits achievement of social/ environmental goals. Other responses: 2 of 8 members voted that the use of e-cigarettes in smokers limits achievement of social/environmental goals. 2 of 8 members voted that the use of e-cigarettes in smokers neither limits or enhances achievement of social/environmental goals. 1 of 8 members voted that the use of e-cigarettes in smokers is not applicable. * with the caveat that carbon neutral vapes do not address this problem.	Members discussed: - Subjectivity of this question; - The available evidence; - Pros and Cons of using e-cigarettes for cessation.	It has been noted that the environmental impacts of e-cigarettes include waste, fires and indoor airborne particulate matter, which, in turn, are likely to have adverse health impacts, the extent of which cannot be determined. (1) It has been reported that the tobacco industry own and produce many of the e-cigarette products on the market (3)(4). Is it appropriate to assume that the tobacco industry would decrease profits if e-cigarettes were to be more regulated and/or banned? Cancer Council NSW noted that there are other Nicotine Replacement Therapies on the market to assist with smoking cessation, such as patches, gum, lozenges, mini-lozenges & inhalers. (5) One report found that the most common messages in online posts about e-cigarettes were found to be about health, safety, and harms. This content typically referred to e-cigarettes as being less harmful than conventional tobacco products. The second most common messages were those promoting the use of e-cigarettes as a smoking cessation tool, and the third were those emphasising certain product types and characteristics such as brands, flavours, and nicotine content. (2) NASEM reported that: (i) there is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels (ii) there is moderate evidence that secondhand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes. (6)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 2. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 3. Greenhalgh EM, Scollo MM and Winstanley MH. , Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021. 4. Bauld L, Angus K, De Andrade M and Ford A. Electronic Cigarette Marketing: Current Research and Policy. *Cancer Research.* 2016. p72. 5. Cancer Council NSW. NRT Factsheet. 2016. https://www.cancercouncil.com.au/wp-content/uploads/2016/09/16138_CA_CAN5084_NRTFactsheet_WEB.pdf. Accessed 3 December 2021. 6. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.
Financial and economic considerations				
Non-smokers	4 out of 8 members agreed that e-cigarettes have a large cost/impact to non-smokers. Other responses: 3 of 8 members voted that e-cigarettes have a moderate cost/impact. 1 of 8 members voted that e-cigarettes have a negligible cost/impact or savings.	Members discussed the financial and economic implications for gateway use, product purchasing, infrastructure and burden.	Is it appropriate to assume that e-cigarettes are more expensive than not buying any at all? Is it appropriate to assume that in most cases e-cigarettes are cheaper to purchase and easily accessible? Is it appropriate to assume that there is an increased burden on schools to provide guidance, information and structures to prevent uptake of children and young adults smoking e-cigarettes? Is it appropriate to assume that Increased burden on parents to educate themselves and their children on the harms of e-cigarettes?	

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	4 out of 8 members agreed that there is negligible cost/impact or savings for smokers. Other responses: 3 of 8 members voted that there is moderate savings for smokers. 1 of 8 members voted that there is moderate cost/impact for smokers.	Members discussed: - Available evidence; - Relative costs compared to burnt tobacco; - Longterm financial cost to smokers quitting combustible cigarettes. - based on current evidence on cessation success, NRTs are likely to provide greater savings to smokers than e-cigarettes as a cessation tool.	The Department of Health estimated that tobacco use in Australia (including health) costs $137 billion in 2015-2016. This included $19.2 billion in tangible costs and $117.7 billion in intangible costs. (1) One study on perceptions and beliefs found that e-cigarettes are often perceived as being cheaper than smoking regular cigarettes. (2) When e-cigarettes are privately imported into Australia, they are not classed as tobacco products and are therefore not subject to customs duty. They are also not subject to GST if their customs value is at or below A$1,000 (3) A cost effective modelling study suggested that a fairly permissive regulatory environment around vaporized nicotine products achieves net health gain and cost savings in New Zealand, albeit with wide uncertainty. (4) Is it appropriate to assume that requiring a prescription from a doctor to access nicotine-containing e-cigarettes makes accessing e-cigarettes more expensive and more difficult than previously importing supply? Is it appropriate to assume that there is a greater burden on Doctors and Pharmacists to manage access the distribution of nicotine-containing e-cigarettes, increasing the overall cost on staff for consultations, training and purchasing a licence to distribute? Is it appropriate to assume that there is an increased burden on schools to provide guidance, information and structures to prevent uptake of children and young adults smoking e-cigarettes?	1. Australian Government Select Committee on Tobacco Harm Reduction. Senate Report. 2020. , https://www.aph.gov.au/Parliamentary_Business/Committees/Senate/Tobacco_Harm_Reduction/TobaccoHarmReduction/Report. Accessed 30 November 2021. 2. Villanti AC, Rath JM, Williams VF, et al. Impact of exposure to electronic cigarette advertising on susceptibility and trial of electronic cigarettes and cigarettes in US young adults: A randomized controlled trial. *Nicotine Tobacco Research.* 2016;18(5):1331-9. 3. Greenhalgh EM, Scollo MM and Winstanley MH. , Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021. 4. Petrović-van der Deen FS, Wilson N, Crothers A, et al. Potential Country-level Health and Cost Impacts of Legalizing Domestic Sale of Vaporized Nicotine Products. *Epidemiology*. 2019;30(3):396-404.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Feasibility and health system considerations				
Non-smokers	5 out of 8 members agreed that e-cigarette use by non-smokers has a negative impact on the current health system infrastructure*. *feasibility to implement was discounted as the CEO Statement will not be developing or implmenting a specific recommendation.	Members discussed: - New Zealands announcement regarding banning tobacco for future generations and the potential impact on the Australian health system; - feasability to implement/impact on the healthcare system of implementing a similar approach in Australia.	The Australian Government Department of Health noted that recent developments suggest the existing regulatory control in Australian that govern the marketing and use of e-cigarettes may not be adequate in protecting the Australian community, particularly children and youth. (1) One report stated that recent research has found that exposure to e-cigarette advertising across a wide range of media is positively associated with e-cigarette status among young people. This finding supports the implementation of appropriate restrictions on e-cigarette marketing to reduce harms among young people. (2) One paper noted that these laws encompass most types of advertising, including print, tv, and radio to point of sale. Additionally, they restrict the display of any e-cigarette product at point of sale, except in Victoria, where certified specialist e-cigarette retailers, defined as businesses whose primary business is the sale of e-cigarettes, can display products in their stores (3) One paper stated that there are regulations at the state and territory level that prohibit the advertising, promotion and sponsorship of both nicotine and non-nicotine containing cigarettes. (2) One paper noted that non-nicotine containing e-cigarettes are legal and easily accessible. However, some liquids labelled non-nicotine have been found to contain nicotine. (4) The sale of all types of e-cigarettes is banned in 30 countries. Overall, 36 countries, including Australia, regulate the concentration/volume of nicotine in e-cigarettes. Thirty four of these countries – including Canada, Israel, Saudi Arabia, England, Scotland, Wales, Northern Ireland and countries in the EU – stipulate an upper limit of 20mg/mL nicotine concentration in e-liquids, Iceland stipulates an upper limit of 20mg/mL with higher concentrations regulated as medicinal products and Australia has an upper limit of 100mg/mL. (5) One report noted that in many countries, e-cigarettes are marketed as aids to smoking cessation – explicitly or implicitly – and, among e-cigarette users, smoking cessation is a commonly reported reason for use. However, 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. (5)	1. Australian Department of Health. Policy and regulatory approach to electronic cigarettes (e-cigarettes) in Australia. 2019., https://www.health.gov.au/resources/publications/policy-and-regulatory-approach-to-electronic-cigarettes-e-cigarettes-in-australia. Accessed 30 November 2021. 2. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 3. Klein D, Chaiton M, Kundu A, et al. A literature review on international e-cigarette regulatory policies. *Current Addiction Reports* 2020; 7:509-19. 4. Chivers E, Janka M, Franklin P, et al. Nicotine and other potentially harmful compounds in "nicotine-free" e-cigarette liquids in Australia. Medical Journal of Australia. 2019;210(3):127-128. 5. Banks E, Buckley N, Day C and 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 narrative review. Draft report for the Australian Government Department of Health. 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	7 out of 8 members agreed that e-cigarette use by smokers has a neutral impact on the current health system infrastructure*. *feasibility to implement was discounted as the CEO Statement will not be developing or implementing a specific recommendation.	Members discussed: - impact of General Practitioner lead cessation; - pros and cons of the prescription method, including difficulties with telehealth (no face-to-face assessment) and that patients are often new to GPs and therefore the patient history is unknown.	The Australian Government Department of Health noted recent developments suggest the existing regulatory control in Australia that govern the marketing and use of e-cigarettes may not be adequate in protecting the Australian community, particularly children and youth. (1) Under the national Therapeutic Goods Act, nicotine containing e-cigarettes are regulated as a prescription medication, and therefore can not be advertised to consumers. (1) One paper stated that there is no direct federal legislation in Australia that directly related to e-cigarettes. E-cigarettes are managed by several existing laws that relate to poisons, tobacco control and therapeutic goods. (2) The Therapeutic Goods Administration stated it is currently in Australia, it is illegal to purchase nicotine-containing e-cigarettes without a prescription from a doctor. Similarly, it is now illegal for consumers to import nicotine vaping products without a valid prescription from a doctor. (3) One report found that the chemicals used in non-nicotine containing e-liquids are regulated as industrial chemicals. These chemicals are assessed through the Australian Industrial Chemicals Introduction Scheme for human health and environmental risks to promote safe use. Nicotine-containing e-cigarette liquids are regulated through TGA and manages their access restrictions through the Poisons Standard. (4) The sale of all types of e-cigarettes is banned in 30 countries. Overall, 36 countries, including Australia, regulate the concentration/volume of nicotine in e-cigarettes. Thirty four of these countries – including Canada, Israel, Saudi Arabia, England, Scotland, Wales, Northern Ireland and countries in the EU – stipulate an upper limit of 20mg/mL nicotine concentration in e-liquids, Iceland stipulates an upper limit of 20mg/mL with higher concentrations regulated as medicinal products and Australia has an upper limit of 100mg/mL (5) Is it appropriate to assume that e-cigarettes have the potential to increase and decrease costs and burden of smoking related illness on the healthcare system?	1. Australian Department of Health. Policy and regulatory approach to electronic cigarettes (e-cigarettes) in Australia. 2019.„ https://www.health.gov.au/resources/publications/policy-and-regulatory-approach-to-electronic-cigarettes-e-cigarettes-in-australia. Accessed 30 November 2021. 2. McCausland K, Maycock B, Leavar T, et al. "Is it banned? Is it illegal?" Navigating Western Australia's regulatory environment for e-cigarettes. *International Journal of Drug Policy*. 2021; 94:103177 3. Therapeutic Goods Administration. *Nicotine vaping product access*, Australian Government. 2021. https://www.tga.gov.au/nicotine-vaping-product-access. Accessed 1 December 2021. 4. National Industrial Chemicals Notification and Assessment Scheme. Non-nicotine liquids for e-cigarette devices in Australia: chemistry and health concerns. 2019. 5. Banks E, Buckley N, Day C and 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 narrative review. Draft report for the Australian Government Department of Health. 2021.
Quality (confidence/certainty) in the evidence				
Outcome: smoking relapse				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	Members noted that this outcome is not applicable to this population group.		Not applicable.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	Members noted that this outcome is not applicable to this population group. Members agreed that former smokers should be its own population. Limitations about the effect or precision of the outcome was noted.	If former smokers are included in the definition for this cohort, 7 out of 9 Survey 2 respondents agreed that there was low certainty evidence that former smokers that are current e-cigarettes users are 2.4 times more likely to relapse than former smokers that have never used e-cigarettes. (1) A recently published systematic review and meta-analysis by Barufaldi et al. (2021) found similar results: former smokers that use e-cigarettes were twice as likely to relapse. (2)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. Barufaldi AL, Guerra RL, de Albuquerque RD, et al. Risk of smoking relapse with the use of electronic cigarettes: A systematic review with meta-analysis of longitudinal studies. *Tobacco Prevention and Cessation.* 2021; 29.
Outcome: smoking cessation				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	Members noted that this outcome is not applicable to this population group.		Not applicable.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	<u>E-cigarettes & cessation</u> Certainty of evidence for smoking cessation varied from very low to low, depending on intervention (for example nicotine e-cigarettes alone, nicotine e-cigarettes and counselling) and comparator (for example, non-nicotine containing e-cigarettes, nicotine replacement therapies) (1 & 1a). There is limited evidence that, in the clinical context in combination with best-practice counselling and supportive care, 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. There is insufficient evidence that 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. There is also insufficient evidence that nicotine e-cigarettes are efficacious outside the clinical setting. (1 & 1a) A systematic review by Cochrane found low certainty evidence that smokers that used nicotine-containing e-cigarettes had increased odds of stopping smoking in the long term compared to using non-nicotine-containing e-cigarettes (2). A report of the UK Royal College of Physicians (20 May 2021) stated that E-cigarettes are an effective treatment for tobacco dependency and their use should be included and encouraged in all treatment pathways. (3). A report by the US Surgeon General stated that there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation. (4) The NASEM report concluded that: (i) there is moderate evidence from randomised controlled trials that e-cigarettes with nicotine are more effective than e-cigarettes without nicotine for smoking cessation (ii) there is moderate evidence from observational studies that more frequent use of e-cigarettes is associated with an increased likelihood of cessation (iii) there is insufficient evidence from randomised controlled trials about the effectiveness of e-cigarettes as cessation aids compared with no treatment or to Food and Drug Administration-approved smoking cessation treatments (iv) overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation. (5) <u>E-cigarette advertising & cessation</u> 5 out of 6 Survey 3 respondents agreed that there was very low certainty evidence that smokers exposed to e-cigarette advertising were 0.85 times (point-of-sale advertising) and 0.92 times (multiple media sources) less likely to quit smoking. Three (3) out of 6 Survey 3 respondents agreed that there was low certainty evidence that smokers exposed to e-cigarette advertising perceived that using e-cigarettes could help with quitting smoking. Five (5) out of 6 Survey 3 respondents agreed that there was very low certainty evidence that individuals exposed to e-cigarette advertising were less likely to have intentions to quit smoking than individuals not exposed to e-cigarette advertising. (6)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. Hartmann-Boyce J, McRobbie H, Butler AR, et al. Electronic cigarettes for smoking cessation. Cochrane Database of Systematic Reviews. 2021; (9). 3. Royal College of Physicians. Smoking and health 2021: a coming of age for tobacco control? 2021. 4. US Department of Health and Human Services. Smoking Cessation. A Report of the Surgeon General. 2020. https://www.hhs.gov/sites/default/files/2020-cessation-sgr-full-report.pdf. Accessed 29 November 2022. 5. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 6. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: smoking uptake/initiation				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	<u>E-cigarettes & combustible smoking uptake/initiation</u> Five (5) out of 9 Survey 2 respondents agreed that there was low certainty evidence that never smokers that use e-cigarettes are 3.14 times more likely to take up combustible smoking than never smokers that do not use e-cigarettes. Six (6) out of 9 Survey 2 respondents agreed that there was very low certainty evidence that non-current smokers that use e-cigarettes are 3.19 times more likely to take up combustible smoking than non-current smokers that do not use e-cigarettes. <u>The NASEM report concluded that:</u> (i) there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults (ii) among youth and young adult e-cigarette users who ever use combustible cigarettes, there is moderate evidence that e-cigarette use increases the frequency and intensity of subsequent combustible tobacco cigarette smoking (iii) among youth and young adult e-cigarette users who ever use combustible tobacco cigarettes, there is limited evidence that e-cigarette use increases, in the near term, the duration of subsequent combustible tobacco cigarette smoking. (2) The SCHEER report stated that overall, that SCHEER is of the opinion that there is moderate evidence that e-cigarettes are a gateway to smoking/for young people. There is also strong evidence that nicotine in e-liquids is implicated in the development of addiction and that flavours have a relevant contribution for attractiveness of use of electronic cigarette and initiation. (3) <u>E-cigarette advertising & combustible smoking uptake/initiation</u> Four (4) out of 6 Survey 3 respondents agreed that there was very low certainty evidence that dual users exposed to e-cigarette advertising were 2.1 times more likely to take up combustible smoking. (4)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021 4. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.		Not applicable.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: cardiovascular health outcomes (clinical & sub-clinical)				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Five (5) out of 7 Survey 4 respondents agreed that no evidence from human epidemiological or clinical trials was available on the effect of e-cigarette use on clinical and sub-clinical cardiovascular health outcomes (1 & 1a). One (1) out of 7 Survey 4 respondents suggested that this should be noted as a priority research area/gap in the evidence. The NASEM report concluded that there is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification). (2) The European Heart Network concluded that there is mixed evidence for the effects of electronic cigarettes on the cardiovascular system from short-term exposure. (3) The European Association of Preventive Cardiology (EAPC) in a recent position paper reported that although the long-term direct cardiovascular effects remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. (4) One study pooled data from the 2016 and 2017 Behavioural Risk Factor Surveillance System and found that in the 449,092 participants there was no association between e-cigarette use and cardiovascular disease in individuals who had never smoked. (5) One cross-sectional study by Alzahrani et al. found Daily e-cigarette use was independently associated with increased odds of having had a myocardial infarction (OR=1.79, 95% CI=1.20, 2.66, p=0.004) (6). This study was included in NCEPH's health outcomes top-up review. (1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a.Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. European Heart Network. Electronic cigarettes and cardiovascular disease – an update from the European Heart Network. 2019. https://ehnheart.org/images/EHN_e-cigarettes_final_final.pdf. Accessed 1 December 2021. 4. Kavousi M, Pisinger C, Barthelemy JC, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *European Journal of Preventative Cardiology*. 2020; 29. 5. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. *American Journal of Medicine*. 2019; 132(8):949-954.e2. 6. Alzahrani T, Pena I, Temesgen N, Glantz S. Association between electronic cigarette use and myocardial infarction. *American Journal of Preventive Medicine*. 2018; 55(4): 455-61.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Five (5) out of 7 Survey 4 respondents agreed that no evidence from human epidemiological or clinical trials was available on the effect of e-cigarette use on clinical and sub-clinical cardiovascular health outcomes (1 & 1a). One (1) out of 7 Survey 4 respondents suggested that this should be noted as a priority research area/gap in the evidence. The NASEM report concluded that there is no available evidence whether or not e-cigarette use is associated with clinical cardiovascular outcomes (coronary heart disease, stroke, and peripheral artery disease) and subclinical atherosclerosis (carotid intima-media thickness and coronary artery calcification). (2) The European Heart Network concluded that there is mixed evidence for the effects of electronic cigarettes on the cardiovascular system from short-term exposure. In particular, it was noted that while some studies have found a higher risk compared to smoking combustible tobacco cigarettes, short-term electronic cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes. (3) EAPC in a recent position paper reported that although the long-term direct cardiovascular effects remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. (4) One study pooled data from the 2016 and 2017 Behavioural Risk Factor Surveillance System and found that in the 449,092 participants, persons who both smoked conventional cigarettes and also used e-cigarettes were more likely to have cardiovascular disease than those who only smoked conventional cigarettes. (5) One cross-sectional study by Alzahrani et al. found Daily e-cigarette use was independently associated with increased odds of having had a myocardial infarction (OR=1.79, 95% CI=1.20, 2.66, p=0.004) as was daily conventional cigarette smoking (OR=2.72, 95% CI=2.29, 3.24, p<0.001) (6). This study was included in NCEPH's health outcomes top-up review. (1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. European Heart Network. Electronic cigarettes and cardiovascular disease – an update from the European Heart Network. 2019. https://ehnheart.org/images/EHN_e-cigarettes_final_final.pdf. Accessed 1 December 2021. 4. Kavousi M, Pisinger C, Barthelemy JC, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *European Journal of Preventative Cardiology*. 2020; 29. 5. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. *American Journal of Medicine*. 2019; 132(8):949-954.e2. 6. Alzahrani T, Pena I, Temesgen N and Glantz S. Association between electronic cigarette use and myocardial infarction. *American Journal of Preventive Medicine*. 2018; 55(4): 455-61.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: other cardiovascular health outcomes (for example, **increased blood pressure, heart rate, endothelial function)**				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Five (5) out of 7 Survey 4 respondents agreed that there was insufficient/very low certainty evidence on the effect of e-cigarette use on other cardiovascular health outcomes. (1 & 1a) The NASEM report concluded that: (i) there is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes (ii) there is limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control (iii) there is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes (iv) There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes (v) there is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function. (2) The European Heart Network concluded that there is mixed evidence for the effects of electronic cigarettes on the cardiovascular system from short-term exposure. In particular, it was noted that while some studies have found a higher risk compared to smoking combustible tobacco cigarettes, short-term electronic cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes. (3) EAPC in a recent position paper reported that although the long-term direct cardiovascular effects remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. (4) One study pooled data from the 2016 and 2017 Behavioural Risk Factor Surveillance System and found that in the 449,092 participants there was no association between e-cigarette use and cardiovascular disease in individuals who had never smoked. (5) A recent systematic review and meta-analysis by Larue et al (2021) found that acute use of nicotine e-cigs was associated with statistically significant cardiovascular and respiratory responses. (6)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a.Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. European Heart Network. Electronic cigarettes and cardiovascular disease – an update from the European Heart Network. 2019. https://ehnheart.org/images/EHN_e-cigarettes_final_final.pdf. Accessed 1 December 2021. 4. Kavousi M, Pisinger C, Barthelemy JC, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *European Journal of Preventative Cardiology*. 2020; 29. 5. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. *American Journal of Medicine*. 2019; 132(8):949-954.e2. 6. Larue F, Tasbih T, Ribeiro PAB, et al. Immediate physiological effects of acute electronic cigarette use in humans: A systematic review and meta-analysis. *Respiratory Medicine*. 2021; ;190:106684.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=7/7) Survey 4 respondents agreed that: (i) there is moderate evidence that e-cigarettes use by smokers is associated with increased heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use (ii) there is limited/low certainty evidence that e-cigarette use by smokers is associated with increased endothelial dysfunction (iii) there is limited/low certainty evidence that e-cigarette use by smokers is associated with decreased blood pressure after long-term use after switching from combustible smoking. (1 & 1a) The NASEM report concluded that: (i) there is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes (ii) there is limited evidence that e-cigarette use is associated with a short-term increase in systolic blood pressure, changes in biomarkers of oxidative stress, increased endothelial dysfunction and arterial stiffness, and autonomic control (iii) there is substantial evidence that heart rate increases shortly after nicotine intake from e-cigarettes (iv) There is moderate evidence that diastolic blood pressure increases shortly after nicotine intake from e-cigarettes (v) there is insufficient evidence that e-cigarette use is associated with long-term changes in heart rate, blood pressure, and cardiac geometry and function. (2) The European Heart Network concluded that there is mixed evidence for the effects of electronic cigarettes on the cardiovascular system from short-term exposure. In particular, it was noted that while some studies have found a higher risk compared to smoking combustible tobacco cigarettes, short-term electronic cigarette use is likely less harmful to the cardiovascular system than smoking conventional cigarettes. (3) EAPC in a recent position paper reported that although the long-term direct cardiovascular effects remain largely unknown, the existing evidence suggests that the e-cigarette should not be regarded as a cardiovascular safe product. (4) One study pooled data from the 2016 and 2017 Behavioural Risk Factor Surveillance System and found that in the 449,092 participants, persons who both smoked conventional cigarettes and also used e-cigarettes were more likely to have cardiovascular disease than those who only smoked conventional cigarettes. (5) A recent systematic review and meta-analysis by Larue et al (2021) found that acute use of nicotine e-cigs was associated with statistically significant cardiovascular and respiratory responses. (6)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. European Heart Network. Electronic cigarettes and cardiovascular disease – an update from the European Heart Network. 2019. https://ehnheart.org/images/EHN_e-cigarettes_final_final.pdf. Accessed 1 December 2021. 4. Kavousi M, Pisinger C, Barthelemy JC, et al. Electronic cigarettes and health with special focus on cardiovascular effects: position paper of the European Association of Preventive Cardiology (EAPC). *European Journal of Preventative Cardiology*. 2020; 29. 5. Osei AD, Mirbolouk M, Orimoloye OA, et al. Association Between E-Cigarette Use and Cardiovascular Disease Among Never and Current Combustible-Cigarette Smokers. *American Journal of Medicine*. 2019; 132(8):949-954.e2. 6. Larue F, Tasbih T, Ribeiro PAB, et al. Immediate physiological effects of acute electronic cigarette use in humans: A systematic review and meta-analysis. *Respiratory Medicine*. 2021; ;190:106684.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: cancer				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and cancer. (1 & 1a) The NASEM report concluded that: (i) there is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products (ii) there is substantial evidence that some chemicals present in e-cigarette aerosols (for example, formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined (iii) there is limited evidence from in vivo animal studies using intermediate biomarkers of cancer to support the hypothesis that long-term e-cigarette use could increase the risk of cancer; there is no available evidence from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk. (2) The World Health Organization (WHO) stated that given the relatively recent entry of ENDS into the market and the lengthy lag time for onset of many diseases of interest, such as cancer, conclusive evidence about the association of ENDS use with such diseases will not be available for years or even decades (3). SCHEER also noted that long term use in relation to lung cancer remained to be determined. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a.Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control; 2016. 4. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and cancer. (1 & 1a) The NASEM report concluded that: (i) there is no available evidence whether or not e-cigarette use is associated with intermediate cancer endpoints in humans. This holds true for e-cigarette use compared with use of combustible tobacco cigarettes and e-cigarette use compared with no use of tobacco products (ii) there is substantial evidence that some chemicals present in e-cigarette aerosols (for example, formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. Whether or not the levels of exposure are high enough to contribute to human carcinogenesis remains to be determined (iii) there is limited evidence from in vivo animal studies using intermediate biomarkers of cancer to support the hypothesis that long-term e-cigarette use could increase the risk of cancer; there is no available evidence from adequate long-term animal bioassays of e-cigarette aerosol exposures to inform cancer risk. (2) The World Health Organization (WHO) stated that given the relatively recent entry of ENDS into the market and the lengthy lag time for onset of many diseases of interest, such as cancer, conclusive evidence about the association of ENDS use with such diseases will not be available for years or even decades (3). SCHEER also noted that long term use in relation to lung cancer remained to be determined. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control; 2016. 4. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: sleep (clinical outcomes)				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and clinical sleep outcomes. (1 & 1a) A literature review by CSIRO found that e-cigarette vapour exposure had significant effects on the offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and clinical sleep outcomes. (1 & 1a) A literature review by CSIRO found that e-cigarette vapour exposure had significant effects on the offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Outcome: wound healing				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and wound healing. (1 & 1a) A literature review by CSIRO found that case studies have suggested that e-cigarette use interferes with, or delays, wound healing. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and wound healing. (1 & 1a) A literature review by CSIRO found that case studies have suggested that e-cigarette use interferes with, or delays, wound healing. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Outcome: endocrine outcomes				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and endocrine outcomes. (1 & 1a) One study found that chronic inhalation of e-cigarette vapour in mice, at a dose equivalent to human use, led to renal dysfunction, fibrosis and increased expression of pro-fibrotic factors. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Crotty Alexander LE, Drummond CA, Hepokoski M, et al. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces systemic inflammation and multiorgan fibrosis in mice. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.* 2018; R834-R847.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and endocrine outcomes. (1 & 1a) One study found that chronic inhalation of e-cigarette vapour in mice, at a dose equivalent to human use, led to renal dysfunction, fibrosis and increased expression of pro-fibrotic factors. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.2. 2.Crotty Alexander LE, Drummond CA, Hepokoski M, et al. Chronic inhalation of e-cigarette vapor containing nicotine disrupts airway barrier function and induces systemic inflammation and multiorgan fibrosis in mice. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology.* 2018; R834-R847

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: allergic diseases				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and allergies/allergic diseases. (1 & 1a) The NASEM review notes that allergic dermatitis has previously been associated with propylene glycol as well as nickel (2) The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 31 chemicals may cause allergic reactions, based on available toxicological assessment data. (3) The CSIRO literature review noted one case report which found that mercaptobenzothiazole (e-cigarette constituent) was a source of allergic reactions which had not previously been referred to in relation to e-cigarettes.(4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021. 4. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and allergies/allergic diseases. (1 & 1a) The NASEM review notes that allergic dermatitis has previously been associated with propylene glycol as well as nickel (2). The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 31 chemicals may cause allergic reactions, based on available toxicological assessment data (3). The CSIRO literature review noted one case report which found that mercaptobenzothiazole (e-cigarette constituent) was a source of allergic reactions which had not previously been referred to in relation to e-cigarettes. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021. 4. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: haematological outcomes				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and haematological outcomes (1 & 1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials on the association between e-cigarette use and haematological outcomes (1 & 1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.
Outcome: respiratory disease - lung damage (EVALI)				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was conclusive/high certainty evidence that e-cigarette use can cause EVALI/lung injury. 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. Case reports, which are ranked as a lower form of evidence on the hierarchy of research designs, typically provide limited evidence of causality. However only case reports where the patients fulfilled the CDC criteria for a probable or confirmed case of EVALI were included in the evidence synthesis. (1 & 1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was conclusive/high certainty evidence that e-cigarette use can cause EVALI/lung injury. 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. Case reports, which are ranked as a lower form of evidence on the hierarchy of research designs, typically provide limited evidence of causality. However only case reports where the patients fulfilled the CDC criteria for a probable or confirmed case of EVALI were included in the evidence synthesis. (1 & 1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: other respiratory disease				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarettes use by non-smokers is associated with other clinical respiratory outcomes (asthma, bronchitis and COPD) or other respiratory measures (sinonasal symptoms, airway hyper-responsiveness) (ii) there is insufficient/very low certainty evidence that e-cigarette use by non-smokers can cause decreased spirometry parameters up to 25minutes post exposure (iii) there is insufficient/very low evidence that e-cigarette use by non-smokers can cause exhaled breath outcomes. (1 & 1a) The NASEM report concluded that: (i) there is limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies (ii) there is no available evidence whether or not e-cigarettes cause respiratory diseases in humans (iii) there is moderate evidence that e-cigarette use results in increased cough and wheeze in adolescents, and an association between e-cigarette use and an increase in asthma exacerbations. (2) SCHEER concluded that the overall weight of evidence is moderate for risks of local irritative damage to the respiratory tract of users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine. However, the overall reported incidence is low (3). The CSIRO literature review found that the use of e-cigarettes may impair lung function however the independent effect of e-cigarettes is unclear because of potential confounding by conventional cigarette smoking (4). One study that examined data from the 2016 Behavioural Risk Factor Surveillance System conducted in Hawaii found that e-cigarette use was associated with respiratory disorder independent of cigarette use and other physical and psychosocial covariates (5). A recent systematic review and meta-analysis by Larue et al (2021) found that acute use of nicotine e-cigs was associated with statistically significant cardiovascular and respiratory responses. It also found that e-cigarette exposure wasn't associated with significant changes in any spirometry measure (6). The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 42 of the chemicals were assessed to be harmful to inhale and 8 assessed as being a respiratory sensitiser, based on available toxicological assessment data (7).	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021 4. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021. 5. Wills TA, Pagano I, Williams RJ and Tam EK. E-cigarette use and respiratory disorder in an adult sample. *Drug and Alcohol Dependence*. 2019; 194:363-70. 6. Larue F, Tasbih T, Ribeiro PAB, et al. Immediate physiological effects of acute electronic cigarette use in humans: A systematic review and meta-analysis. *Respiratory Medicine*. 2021; ;190:106684. 8. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is insufficient/very low certainty evidence that e-cigarette use by smokers (asthmatic, COPD health smokers) can cause a reduction in respiratory exacerbations (ii) there is insufficient/very low certainty evidence that e-cigarette use by smokers can cause decreased spirometry parameters up to 25minutes post exposure (iii) there is limited/low certainty evidence that e-cigarette use by smokers can cause increased respiratory resistance and impedance up to 30 minutes post exposure (iv) there is insufficient/very low certainty evidence that e-cigarette use by smokers (healthy & asthmatic) can cause exhaled breath outcomes. (1 & 1a) The NASEM report concluded that: (i) there is limited evidence of adverse effects of e-cigarette exposure on the respiratory system from animal and in vitro studies (ii) there is no available evidence whether or not e-cigarettes cause respiratory diseases in humans (iii) there is limited evidence for reduction of chronic obstructive pulmonary disease (COPD) exacerbations among adult smokers with COPD who switch to e-cigarettes completely or in part (dual use) (iv) there is limited evidence for improvement in lung function and respiratory symptoms among adult smokers with asthma who switch to e-cigarettes completely or in part (dual use). (2) SCHEER concluded that the overall weight of evidence is moderate for risks of local irritative damage to the respiratory tract of users of electronic cigarette due to the cumulative exposure to polyols, aldehydes and nicotine. However, the overall reported incidence is low (3). The CSIRO literature review found that the use of e-cigarettes may impair lung function however the independent effect of e-cigarettes is unclear because of potential confounding by conventional cigarette smoking (4). One study that examined data from the 2016 Behavioural Risk Factor Surveillance System conducted in Hawaii found that e-cigarette use was associated with respiratory disorder independent of cigarette use and other physical and psychosocial covariates (5). A systematic review and meta-analysis by Larue et al (2021) found that acute use of nicotine e-cigs was associated with statistically significant cardiovascular and respiratory responses. It also found that e-cigarette exposure wasn't associated with significant changes in any spirometry measure. (6) The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 42 of the chemicals were assessed to be harmful to inhale and 8 assessed as being a respiratory sensitiser, based on available toxicological assessment data. (7)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021 4. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021. 5. Wills TA, Pagano I, Williams RJ and Tam EK. E-cigarette use and respiratory disorder in an adult sample. *Drug and Alcohol Dependence*. 2019; 194:363-70. 6. Larue F, Tasbih T, Ribeiro PAB, et al. Immediate physiological effects of acute electronic cigarette use in humans: A systematic review and meta-analysis. *Respiratory Medicine*. 2021; ;190:106684. 7. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: oral health				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarettes use can cause clinical or intermediated/subclinical oral health outcomes (ii) there is insufficient/very low certainty evidence that e-cigarette use can cause increased gum disease, bone loss around the teeth and any periodontal disease. (1 & 1a) The NASEM report concluded that: (i) there is limited evidence suggesting that nicotine- and non-nicotine–containing e-cigarette aerosol can adversely affect cell viability and cause cell damage of oral tissue in non-smokers. (2) The CSIRO literature review noted that cross sectional studies showed a relationship between e-cigarette use and some types of oral mucosal lesions (OML). More studies on OML and e-cigarette use are required. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarettes use can cause clinical or intermediated/subclinical oral health outcomes (ii) there is insufficient/very low certainty evidence that e-cigarette use can cause increased gum disease, bone loss around the teeth and any periodontal disease (iii) there is insufficient/very low certainty evidence that e-cigarette use can cause reduced plaque, gingival and papillary bleeding in smokers that switched to e-cigarette use. (1 & 1a) The CSIRO literature review noted that cross sectional studies showed a relationship between e-cigarette use and some types of oral mucosal lesions (OML). More studies on OML and e-cigarette use are required. (2)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: developmental and reproductive effects				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarettes use is associated with development (fetal, children & adolescents) and other reproductive outcomes (ii) there is insufficient/very low certainty evidence that e-cigarette use can cause adverse fetal pregnancy outcomes (low birth weight, preterm birth, low Apgar score and small-for-gestational-age) (1 & 1a) The NASEM report concluded that: (i) there is no available evidence whether or not e-cigarettes affect pregnancy outcomes (ii) there is insufficient evidence whether or not maternal e-cigarette use affects fetal development (iii) there was substantial evidence that some chemicals present in e-cigarette aerosols (for example, formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. (2) The CSIRO literature review noted that e-cigarette vapour exposure had significant effects on offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects. (3)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarettes use is associated with development (fetal, children & adolescents) and other reproductive outcomes (ii) there is insufficient/very low certainty evidence that e-cigarette use can cause adverse fetal pregnancy outcomes (low birth weight, preterm birth, low Apgar score and small-for-gestational-age) (1 & 1a) The NASEM report concluded that: (i) there is no available evidence whether or not e-cigarettes affect pregnancy outcomes (ii) there is insufficient evidence whether or not maternal e-cigarette use affects fetal development (iii) there was substantial evidence that some chemicals present in e-cigarette aerosols (for example, formaldehyde, acrolein) are capable of causing DNA damage and mutagenesis. This supports the biological plausibility that long-term exposure to e-cigarette aerosols could increase risk of cancer and adverse reproductive outcomes. (2) The CSIRO literature review noted that e-cigarette vapour exposure had significant effects on offspring of exposed pregnant mice and frog embryos including increased release of pro-inflammatory cytokines, sleep disturbances and craniofacial defects. (3)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: burns and injuries				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that use of e-cigarettes can cause burns and injuries. (1 & 1a) The NASEM report concluded that there is conclusive evidence that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly, or modified by users (2). SCHEER concluded that the overall weight of evidence for risks of poisoning and injuries due to burns and explosion, is strong. However, the incidence is low. (3)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that use of e-cigarettes can cause burns and injuries. (1 & 1a) The NASEM report concluded that there is conclusive evidence that e-cigarette devices can explode and cause burns and projectile injuries. Such risk is significantly increased when batteries are of poor quality, stored improperly, or modified by users (2). SCHEER concluded that the overall weight of evidence for risks of poisoning and injuries due to burns and explosion, is strong. However, the incidence is low. (3)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: poisonings				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that use of e-cigarettes can cause (intentional or accidental) poisoning via nicotine e-liquids and nicotine toxicity. (1 & 1a) A study by Wylie et al (2019) reported that calls to Australian Poisons Information Centres regarding e-cigarette exposures increased substantially between 2012 and 2016. Of the calls reported, 38% were regarding children exposed to e-cigarette liquids, and the remaining 62% were in relation to the exposure of adolescents or adults. Adverse effects appear to be the result of nicotine present in e-cigarette liquids and are described as gastrointestinal disturbances and sedation. The report also notes the death of an infant in Australia from ingestion of nicotine containing liquid (2). SCHEER concluded that the overall weight of evidence for risks of poisoning and injuries due to burns and explosion, is strong. However, the incidence is low. (3) NASEM concluded that: (i) there is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis (ii) there is conclusive evidence that intentionally or unintentionally drinking or injecting e-liquids can be fatal. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Wylie C, Heffernan A, Brown JA, et al. Exposures to e-cigarettes and their refills: calls to Australian Poisons Information Centres, 2009–2016. *Medical Journal of Australia*. 2019; 210(3):126. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021 4. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that use of e-cigarettes is can cause (intentional or accidental) poisoning via nicotine e-liquids and nicotine toxicity. (1) A study by Wylie et al (2019) reported that calls to Australian Poisons Information Centres regarding e-cigarette exposures increased substantially between 2012 and 2016. Of the calls reported, 38% were regarding children exposed to e-cigarette liquids, and the remaining 62% were in relation to the exposure of adolescents or adults. Adverse effects appear to be the result of nicotine present in e-cigarette liquids and are described as gastrointestinal disturbances and sedation. The report also notes the death of an infant in Australia from ingestion of nicotine containing liquid (2). SCHEER concluded that the overall weight of evidence for risks of poisoning and injuries due to burns and explosion, is strong. However, the incidence is low. (3) NASEM concluded that: (i) there is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis (ii) there is conclusive evidence that intentionally or unintentionally drinking or injecting e-liquids can be fatal. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Wylie C, Heffernan A, Brown JA, et al. Exposures to e-cigarettes and their refills: calls to Australian Poisons Information Centres, 2009–2016. *Medical Journal of Australia*. 2019; 210(3):126. 3. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021 4. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: mental health				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarette use can cause clinical mental health outcomes or other mental health outcomes (ii) there is insufficient/very low certainty evidence that e-cigarette use is associated with depressive symptoms. (1 & 1a) The CSIRO literature review notes that results from single studies suggest that more needs to be understood about the relationship between depression and use of e-cigarettes in smokers. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is no available evidence from human epidemiological or clinical trials that e-cigarette use can cause clinical mental health outcomes or other mental health outcomes; (ii) there is insufficient/very low certainty evidence that e-cigarette use is associated with depressive symptoms. (1 & 1a) The CSIRO literature review notes that results from single studies suggest that more needs to be understood about the relationship between depression and use of e-cigarettes in smokers. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021.
Outcome: environmental health				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that e-cigarette use can cause increased airborne particulate matter in indoor environments; (ii) there is limited/low certainty evidence that e-cigarette use can cause concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces; (iii) there is insufficient/very low certainty evidence that e-cigarette use can cause increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls; and (iv) there is substantial/high certainty evidence that e-cigarettes are can cause fires and environmental waste. Five (5) out of 6 Survey 4 respondents agreed that there is insufficient/very low evidence that e-cigarette related environmental hazards can present a hazard to human health. (1 & 1a) The NASEM review concluded that: (i) there is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels; and (ii) there is moderate evidence that second-hand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that: (i) there is conclusive/high certainty evidence that e-cigarette use can cause increased airborne particulate matter in indoor environments; (ii) there is limited/low certainty evidence that e-cigarette use can cause concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces; (iii) there is insufficient/very low certainty evidence that e-cigarette use can cause increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls; and (iv) there is substantial/high certainty evidence that e-cigarettes are can cause fires and environmental waste. Five (5) out of 6 Survey 4 respondents agreed that there is insufficient/very low evidence that e-cigarette related environmental hazards can present a hazard to human health. (1 & 1a) The NASEM review concluded that: (i) there is conclusive evidence that e-cigarette use increases airborne concentrations of particulate matter and nicotine in indoor environments compared with background levels; and (ii) there is moderate evidence that second-hand exposure to nicotine and particulates is lower from e-cigarettes compared with combustible tobacco cigarettes. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018.
Outcome: neurological outcomes				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Five (5) out of 6 Survey 4 respondents agreed that there was conclusive/high certainty evidence that use of e-cigarettes can cause seizures. All (n=6/6) Survey 4 respondents agreed that there was limited/low certainty evidence that use of e-cigarettes can cause nerve damage via explosions, and that there was no available evidence from human epidemiological or clinical trials that the use of e-cigarettes is associated with other clinical neurological outcomes. (1 & 1a) Other reviews found that the association between e-cigarettes and seizures was as a result of poisonings via e-liquids rather than use of e-cigarettes. For example, the NASEM review concluded that there is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis (2). The CSIRO review noted that death from e-cigarette liquid ingestion is very rare, and that it was more common that e-liquid ingestion causes extreme drowsiness, confusion, cardiac arrests and seizures (3). The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 8 of the chemicals were assessed to be a potential risk for neurological health outcomes, based on available toxicological assessment data. (4)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021. 4. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Five (5) out of 6 Survey 4 respondents agreed that there was conclusive/high certainty evidence that use of e-cigarettes can cause seizures. All (n=6/6) Survey 4 respondents agreed that there was limited/low certainty evidence that use of e-cigarettes can cause nerve damage via explosions, and that there was no available evidence from human epidemiological or clinical trials that the use of e-cigarettes is associated with other clinical neurological outcomes. (1 & 1a) Other reviews found that the association between e-cigarettes and seizures was as a result of poisonings via e-liquids rather than use of e-cigarettes. For example, the NASEM review concluded that there is conclusive evidence that intentional or accidental exposure to e-liquids (from drinking, eye contact, or dermal contact) can result in adverse health effects including but not limited to seizures, anoxic brain injury, vomiting, and lactic acidosis (2). The CSIRO review noted that death from e-cigarette liquid ingestion is very rare, and that it was more common that e-liquid ingestion causes extreme drowsiness, confusion, cardiac arrests and seizures (3). The toxicology review report found that of the 369 chemicals identified as currently being used in e-cigarettes or in e-liquids, 8 of the chemicals were assessed to be a potential risk for neurological health outcomes, based on available toxicological assessment data. (4)	1. Yazidjoglou A, Ford L, Baenziger O, et al. Efficacy of e-cigarettes as aids to cessation of combustible tobacco smoking: updated evidence review. Report for the Australian Department of Health. 2021. https://openresearch-repository.anu.edu.au/handle/1885/247864. Accessed 23 September 2021. 1a. Banks E, Beckwith K, Yazidjoglou A, et al. Supplementary Report One: Additional material on the review of evidence on the relationship of e-cigarette use to smoking behaviour, including uptake and cessation. Final report to the National Health and Medical Research Council. June 2021. 2. National Academies of Sciences Engineering and Medicine. Public health consequences of e-cigarettes. Washington, DC: The National Academy Press; 2018. 3. Commonwealth Scientific and Industrial Research Organisation. E-cigarettes, smoking and health. 2018. https://www.csiro.au/en/research/health-medical/diseases/health-impacts-of-electronic-cigarettes. Accessed 1 December 2021. 4. National Health and Medical Research Council. Toxicology of non-nicotine e-cigarette constituents: a snapshot of the evidence base (draft report). 2021.
Outcome: less serious adverse events				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was moderate certainty evidence that use of e-cigarettes can cause less serious adverse events (for example, throat irritation, cough, dizziness, headache and nausea). (1 & 1a) SCHEER concluded that the overall weight of evidence is moderate for risk of local irritative damage to the respiratory tract of electronic cigarette users due to the cumulative exposure to polyols, aldehydes and nicotine. Specifically that in cohort studies, mouth and throat irritation, dissipating over time, was the most frequently reported adverse effect in electronic cigarette users. The overall reported incidence was low (moderate weight of evidence). SCHEER also concluded that the overall weight of evidence is moderate for risk of local irritative damage to the respiratory tract for those that experience second-hand exposure to e-cigarettes. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was moderate certainty evidence that use of e-cigarettes can cause less serious adverse events (for example, throat irritation, cough, dizziness, headache and nausea). (1 & 1a) SCHEER concluded that the overall weight of evidence is moderate for risk of local irritative damage to the respiratory tract of electronic cigarette users due to the cumulative exposure to polyols, aldehydes and nicotine. Specifically that in cohort studies, mouth and throat irritation, dissipating over time, was the most frequently reported adverse effect in electronic cigarette users. The overall reported incidence was low (moderate weight of evidence). SCHEER also concluded that the overall weight of evidence is moderate for risk of local irritative damage to the respiratory tract for those that experience second-hand exposure to e-cigarettes. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021
Outcome: optical health				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials that e-cigarettes can cause clinical optical outcomes or other optical outcomes. All respondents agreed that there was insufficient/very low certainty evidence that e-cigarette use can cause corneal epithelial thickness or pre-corneal tear film stability. (1 & 1a) A recent review by Miglio et al (2021) found that e-cigarette smoking affects tear film, similar to that of active combustible smoking. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Miglio, F, Shehzad N, Zeri F, et al. The effect of active smoking, passive smoking, and e-cigarettes on the tear film: An updated comprehensive review. *Experimental Eye Research*. 2021; 108691.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials that e-cigarettes can cause clinical optical outcomes or other optical outcomes. All respondents agreed that there was insufficient/very low certainty evidence that e-cigarette use can cause corneal epithelial thickness or pre-corneal tear film stability. (1 & 1a) A recent review by Miglio et al (2021) found that e-cigarette smoking affects tear film, similar to that of active combustible smoking. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.Health and Medical Research Council. November 2021. 2. Miglio F, Shehzad N, Zeri F, et al. The effect of active smoking, passive smoking, and e-cigarettes on the tear film: An updated comprehensive review. *Experimental Eye Research*. 2021; 108691.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: olfactory outcomes				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials that e-cigarettes can cause clinical olfactory outcomes. All respondents agreed that there was insufficient/very low certainty evidence that e-cigarette use can cause olfactory measures. (1 & 1a)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	All (n=6/6) Survey 4 respondents agreed that there was no available evidence from human epidemiological or clinical trials that e-cigarettes can cause clinical olfactory outcomes. All respondents agreed that there was insufficient/very low certainty evidence that e-cigarette use can cause olfactory measures. (1 & 1a) A cross-sectional study by Gucht et al (2017) found that conventional smokers reported improved sense of taste and smell when they switched to e-cigarettes. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Gucht, GV, Adriaens K and Baeyens F. Online Vape Shop Customers Who Use E-Cigarettes Report Abstinence from Smoking and Improved Quality of Life, But a Substantial Minority Still Have Vaping-Related Health Concerns. *International Journal Environment of Respiratory Public Health.* 2017; 14(7).

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: impact of e-cigarette advertising				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	E-cigarette advertising via social media, television and movies are not covered by the current advertising regulatory approaches in Australia. As such, is it appropriate to consider (or prioritise) the evidence for the following social media, television and movies? All (n=6/6) Survey 3 respondents agreed that there was moderate certainty evidence that: (i) exposure to e-cigarette advertising occurred both actively and passively, resulting in changed perceptions of the risk profile of e-cigarettes; and (ii) strategies used to enhance the appeal and believability of advertisements are effective in influencing perceptions. Five (5) out of 6 Survey 3 respondents agreed that there was low certainty evidence that: (i) exposure to individuals doing 'vape tricks' on social media can result in beliefs that using e-cigarettes was 'trendy,' 'cool', and 'fun'. From the Survey 3 results, overall, respondents agreed that there was very low certainty evidence that individuals exposed to e-cigarette advertising via television and television and movies were more likely to have intentions to use e-cigarettes, initiate e-cigarette use, be an ever e-cigarette user, be a current eicgarette user, have a higher frequency of use of e-cigarettes or combustible cigarettes, be a current combustible cigarette user, have positive attitudes towards e-cigarettes, consider e-cigarettes as acceptable or perceive e-cigarettes as safe. From the Survey 3 results, overall, most respondents agreed that there was very low certainty evidence that individuals exposed to e-cigarette advertising via social media were more likely to have intentions to use e-cigarettes, be an ever e-cigarette user, be a current eicgarette user, have positive or normative attitudes towards e-cigarettes or perceive e-cigarettes as safe. Four (4) out of 6 Survey 3a respondents and 3 out of 6 of Survey 3b respondents agreed that there was moderate certainty evidence that individuals exposed to e-cigarette advertising via social media were more likely to initiate e-cigarette use. WHO recommends that any form of ENDS advertising, promotion and sponsorship must be regulated by an appropriate governmental body. If this is not possible, an outright ban on ENDS advertising, promotion and sponsorship is preferable to the implementation of voluntary codes on ENDS marketing, given the overwhelming evidence that similar codes for tobacco and alcohol products have failed to protect young people from such advertising. WHO also provides recommended guidance on what should/should not be included in ENDS advertising, sponsorship and promotion. (2) A robust body of research has concluded that tobacco companies have engaged in widespread marketing activity that exerts an influence on young people; exposure to such marketing and other portrayals of smoking in the media and popular culture causes smoking uptake. A growing body of research has been documenting similarly extensive marketing of e-cigarette products and exploring how it might affect use of e-cigarettes, particularly among young people and never smokers. (3)	1. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 2. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control; 2016. 3. Greenhalgh EM, Scollo MM and Winstanley MH. Tobacco in Australia: Facts and issues. 2021. https://www.tobaccoinaustralia.org.au/home.aspx. Accessed 30 November 2021.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	E-cigarette advertising via social media, television and movies are not covered by the current advertising regulatory approaches in Australia. As such, is it appropriate to consider (or prioritise) the evidence for the following social media, television and movies? All (n=6/6) Survey 3 respondents agreed that there was moderate certainty evidence that: (i) exposure to e-cigarette advertising occurred both actively and passively, resulting in changed perceptions of the risk profile of e-cigarettes; and (ii) strategies used to enhance the appeal and believability of advertisements are effective in influencing perceptions Five (5) out 6 Survey 3 respondents agreed that there was low certainty evidence that: (i) exposure to individuals doing 'vape tricks' on social media can result in beliefs that using e-cigarettes was 'trendy,' 'cool', and 'fun'. From the Survey 3 results, overall, respondents agreed that there was very low certainty evidence that individuals exposed to e-cigarette advertising via television and television and movies were more likely to have intentions to use e-cigarettes, initiate e-cigarette use, be an ever e-cigarette user, be a current e-cigarette user, have a higher frequency of use of e-cigarettes or combustible cigarettes, be a current combustible cigarette user, have positive attitudes towards e-cigarettes, consider e-cigarettes as acceptable or perceive e-cigarettes as safe. From the Survey 3 results, overall, most respondents agreed that there was very low evidence that individuals exposed to e-cigarette advertising via social media were more likely to have intentions to use e-cigarettes, be an ever e-cigarette user, be a current e-cigarette user, have positive or normative attitudes towards e-cigarettes or perceive e-cigarettes as safe. Four (4) out of 6 Survey 3a respondents and 3 out of 6 Survey 3b respondents agreed that there was moderate certainty evidence that individuals exposed to e-cigarette advertising via social media were more likely to initiate e-cigarette use. WHO recommends that any form of ENDS advertising, promotion and sponsorship must be regulated by an appropriate governmental body. If this is not possible, an outright ban on ENDS advertising, promotion and sponsorship is preferable to the implementation of voluntary codes on ENDS marketing, given the overwhelming evidence that similar codes for tobacco and alcohol products have failed to protect young people from such advertising. WHO also provides recommended guidance on what should/should not be included in ENDS advertising, sponsorship and promotion. (2)	1. Moola S, Tyagi J, Miller M, et al. The effects of e-cigarette advertising, promotion, and sponsorship on people's attitudes, beliefs and perceptions, intentions, and behaviours: a mixed methods systematic review. Sydney, Australia. 2021. 2. World Health Organization. Electronic nicotine delivery systems and electronic non-nicotine delivery systems (ENDS/ENNDS). Geneva: WHO Framework Convention on Tobacco Control; 2016.

Criteria	Decisions from meeting 5	Committee comments from Meeting 5	Contextual information provided to facilitate discussion (based on WHO-INTEGRATE sub-criteria)	References for contextual information
Outcome: Dependence and abuse liability				
Non-smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Six (6) out of 7 Survey 4 respondents agreed that there is substantial/high certainty evidence that e-cigarette use by non-smokers can cause dependency on e-cigarettes. (1 & 1a) The NASEM report concludes that: (i) there is substantial evidence that e-cigarette use can results in symptoms of dependence on e-cigarettes (ii) there is moderate evidence that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes (iii) there is moderate evidence that variability in e-cigarette product characteristics (nicotine concentration, flavouring, device type, and brand) is an important determinant of risk and severity of e-cigarette dependence. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021. 2. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021
Smokers	Members agreed that evidence statements should be generated out-of-session for consideration and decision. Final evidence statements can be found at *Appendix C*	No additional comments noting that evidence statements will be finalised out-of-session.	Six (6) out of 7 Survey 4 respondents agreed that there is limited/low certainty of evidence that e-cigarette use by -smokers can cause dependency on e-cigarettes. All (n=7/7) respondents agreed that there was insufficient/very low evidence that smokers that use e=cigarettes with variations in flavour and nicotine concentration are more likely to be at risk for abuse liability. (1 & 1a) The NASEM report concludes that: (i) there is substantial evidence that e-cigarette use results in symptoms of dependence on e-cigarettes (ii) there is moderate evidence that risk and severity of dependence are lower for e-cigarettes than combustible tobacco cigarettes (iii) there is moderate evidence that variability in e-cigarette product characteristics (nicotine concentration, flavouring, device type, and brand) is an important determinant of risk and severity of e-cigarette dependence. (2)	1. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: systematic review of global evidence. Report for the Australian Department of Health. 2021. 1a. Banks E, Yazidjoglou A, Beckwith K, et al. 2021. Supplementary Report Two: Additional material on the review of evidence on the health outcomes of e-cigarette exposure. Final report to the National Health and Medical Research Council. November 2021.. 2. Scientific Committee on Health Environmental and Emerging Risks (SCHEER). SCHEER (Scientific Committee on Health Environmental and Emerging Risks) Scientific Opinion on electronic cigarettes. 2021. https://ec.europa.eu/health/system/files/2021-04/scheer_o_017_0.pdf. Accessed 31 July 2021

Appendix C: Evidence statements

Evidence statements: e-cigarette use and combustible smoking uptake and cessation

Survey 2 had a 90% response rate (n=9 out of 10 Committee members).

Table 1: Summary of certainty of evidence assessments by outcome/exposure and evidence statements

PICO ref.^	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence				Study type	Final evidence statement
					Evidence review	Survey 2	Agreement with Survey 2*	Rationale for differing certainty of evidence		
Smoking uptake/initiation										
1.1	Smoking initiation	Never smokers	Users of e-cigarettes	Non-users of e-cigarettes	Strong‡	Low	n=5/9	Majority of the Committee agreed to downgrade from 'moderate' to low' due to serious inconsistency and publication bias. Namely, high heterogeneity and asymmetrical funnel plot.	Cohort & RCTs	There is low certainty of evidence that use of e-cigarettes by never smokers may result in combustible cigarette smoking uptake compared with never smokers that do not use e-cigarettes (OR 3.19; 95% CI: 2.44-4.16; 17 studies).
1.2	Current (past 30 day) smoking	Non-current smokers	Current e-cigarette users	Non-current e-cigarette users	Strong‡	Very low	n=6/9	Majority of the Committee agreed to downgrade from 'low' to 'very low' due to serious risk of bias, inconsistency, indirectness and publication bias. Namely, confounding (inappropriate populations examined), small study size, high heterogeneity and indirectness (US study population).	Cohort	The evidence is very uncertain about the effect of current e-cigarette use by non-current smokers on current (past 30 day) smoking compared with non-current e-cigarette users (OR 3.14; 95% CI: 1.93 – 5.11; 8 studies).
1.3	Smoking relapse	Former smokers	Current e-cigarette users	Never e-cigarette users	Limited‡	Low	n=7/9	Majority of the Committee agreed to downgrade from 'moderate' to low' due to serious risk of bias. Namely, confounding and participant selection.	Cohort	There is low certainty of evidence that use of e-cigarettes by former smokers may result in smoking relapse compared with former smokers that never use e-cigarettes (OR 2.40; 95% CI: 1.50-3.83; 3 studies).
Smoking cessation										
2.1	Smoking cessation	Current smokers	Nicotine e-cigarettes	No smoking cessation aid	Limited‡	Low	n=8/9	Majority of the Committee agreed that the certainty of evidence was 'low' due to serious indirectness and publication bias.	RCTs	There is low certainty of evidence that nicotine e-cigarette use by current smokers may result in a slight increase in smoking cessation compared with current smokers that do not use any smoking cessation aids (RR 2.30; 95% CI: 1.19-4.42; 5 studies).
2.2	Smoking cessation	Current smokers	Nicotine e-cigarettes	Non-nicotine e-cigarettes	Insufficient‡	Low	n=8/9	Majority of the Committee agreed that the certainty of evidence was 'low' due to serious risk of bias and indirectness.	RCTs	There is low certainty of evidence that nicotine e-cigarette use by current smokers may result in little to no difference in smoking cessation compared with current smokers that use non-nicotine e-cigarettes (RR 1.61; 95% CI: 0.98 – 2.65; 4 studies).
2.3	Smoking cessation	Current smokers	Nicotine e-cigarettes (no defined concentration)	Other nicotine replacement therapies (NRTs)	Insufficient‡	Very low	n=8/9	Not applicable	RCTs	The evidence is very uncertain about the effect of nicotine e-cigarette use by current smokers on smoking cessation compared with current smokers that use other nicotine replacement therapies (RR 1.25; 95% CI: 0.74 – 2.11; 3 studies).
2.4	Smoking cessation	Current smokers	Nicotine e-cigarettes (dose >0.01 mg/ml)	Other NRTs	Limited‡	Moderate	n=4/9**	Majority (n=5/9) of the Committee agreed that the certainty of evidence was 'low' due to serious indirectness and imprecision (small number of studies; n=2).	RCTs	There is low certainty of evidence that use of nicotine e-cigarettes (dose >0.01mg/ml) by current smokers may result in little to no difference in smoking cessation compared to current smokers that use other nicotine replacement therapy (RR 1.67; 95% CI: 1.21 – 2.28; 2 studies).

PICO ref.^	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence				Study type	Final evidence statement
					Evidence review	Survey 2	Agreement with Survey 2*	Rationale for differing certainty of evidence		
2.5	Smoking cessation	Current smokers	Nicotine e-cigarettes + NRTs	Other comparators	Insufficient‡	Very low	n=9/9	Not applicable	RCTs	The evidence is very uncertain about the effect of nicotine e-cigarette use in combination with nicotine replacement therapies among current smokers compared to other comparators (pooled measure of effect unavailable).
2.6	Smoking cessation	Current smokers	Non-nicotine e-cigarettes + counselling	Counselling only	Insufficient‡	Low	n=6/9	Majority of the Committee agreed that the certainty of evidence was 'low' due to very serious risk of bias, and serious indirectness and imprecision.	RCTs	There is low certainty of evidence that use of non-nicotine e-cigarettes and counselling by current smokers may result in little to no difference in smoking cessation compared to current smokers that used counselling alone (RR 1.70; 95% CI: 0.75 – 3.89; 2 studies).
2.7	Smoking cessation	Current smokers	Non-nicotine e-cigarettes	Other NRTs	Insufficient‡	Low	n=6/9	Majority of the Committee agreed that the certainty of evidence was 'low' due to serious indirectness and publication bias, and very serious imprecision (data from one study).	RCTs	Evidence from a single study suggests that use of non-nicotine e-cigarettes by current smokers may result in little to no difference in smoking cessation compared to current smokers that use other nicotine replacement therapies (RR 0.71; 95% CI: 0.21 – 2.37; 1 study).

^ PICO reference number is unique to each table and may not be consistent across various documents.
* proportion of survey respondents that agreed to the certainty of evidence statement as presented in Survey 2.
** as per Appendix A of the Evidence to Decision report, 5/9 respondents thought the certainty of evidence should be low. We have used 'low certainty of evidence' to inform the evidence statement.
‡ The quality assessment used in the evidence review for these outcomes was the Newcastle-Ottawa Scale.

Evidence statements: effects of e-cigarette advertising, promotion and sponsorship

Surveys 3a and 3b had a 60% response rate (n=6 out of 10 Committee members).

Table 2: Summary of certainty of evidence assessments by outcome/exposure and evidence statements

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
Intentions to use e-cigarettes												
1.1	Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Billboard/poster - exposure	Billboard/poster – no exposure	Not specified for secondary outcomes	Very low	n=6/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effect of e-cigarette advertising via billboard/posters among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via billboards/posters (OR 1.22; 95% CI: 0.87 – 1.72; 2 studies).
1.2	Intentions to use e-cigarettes	Adolescents – smoking status not specified	Internet advertising - exposure	Internet advertising – no exposure	Not specified for secondary outcomes	Very low	n=5/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via the internet among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via the internet (OR 1.80; 95% CI: 1.28 – 2.54; 3 studies).
1.3	Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	Not specified for secondary outcomes	Very low	n=6/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents on intentions to use e-cigarettes compared with no/rare exposure to e-cigarette advertising via multiple media sources (OR 1.28; 95% CI: 1.04 – 1.58; 2 studies).
1.4	Intentions to use e-cigarettes	Adolescents and young adults	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	Not specified for secondary outcomes	Very low	n=6/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effects of e-cigarette advertising via multiple media sources among adolescents and young adults on intentions to use e-cigarettes compared with no/rare exposure to e-cigarette advertising via multiple media sources (OR 1.11; 95% CI: 1.08 – 1.14; 2 studies).
1.5	Intentions to use e-cigarettes	Adolescents – smoking status not specified	Print media - exposure	Print media – no exposure	Not specified for secondary outcomes	Very low	n=4/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effects of e-cigarette advertising via print media among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via print media (OR 1.24; 95% CI: 1.13 – 1.35; 2 studies).

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
1.6	Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Radio advertising - exposure	Radio advertising – no exposure	Not specified for secondary outcomes	Very low	n=6/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effects of e-cigarette advertising via radio among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via ratio (OR 1.36; 95% CI: 0.92 – 2.01; 2 studies).
1.7	Intentions to use e-cigarettes	Adolescents - never, ever and current e-cigarette users, and never users of combustible cigarettes	Television advertising - exposure	Television advertising – no exposure	Not specified for secondary outcomes	Very low	n=6/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effects of e-cigarette advertising via television among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via television (OR 1.41; 95% CI: 1.02 – 1.94; 2 studies)
1.8	Intentions to use e-cigarettes	Young adults – Never e-cigarette users and less than 100 cigarettes smoked in lifetime	Multiple media advertising - exposure to ads that promoted e-cigs as cessation aids	Multiple media advertising – exposure to control advertisements (of everyday items; ie, did not promote e-cigs)	Not specified for secondary outcomes	-	-	Moderate	n=1/6**	Majority of the Committee agreed that the certainty of evidence was 'very low' due to serious risk of bias, indirectness and imprecision.	RCT	The evidence from a single study suggests that e-cigarette advertising via multiple media sources among young adults may result in an increase in intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via multiple media sources (standardised regression coefficients 0.05; SE 0.02, p = 0.04; 1 study).
E-cigarette uptake/initiation												
2.1	E-cigarette uptake/initiation	Adolescents – never smokers/e-cig users	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	Moderate	Low	n=6/6	-	-	The Committee agreed that bodies of evidence that consist of prospective cohort studies will assume an initial level of confidence of "MODERATE". The Committee agreed that the certainty of evidence was 'low' due to serious risk of bias and indirectness.	Cohort	There is low certainty of the evidence that e-cigarette advertising via multiple media sources among adolescents most of the time/always/sometimes may result in a slight increase in e-cigarette uptake/initiation compared with exposure to e-cigarette advertising via multiple media sources never/rarely (OR: 1.64; 95% CI: 1.45 – 1.86; 3 studies).

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
2.2	E-cigarette uptake/initiation	Adolescents – smoking status not specified	Multiple media sources – (greater) exposure	Multiple media sources – no exposure	Low	Very low	n=6/6	-	-	The Committee agreed that bodies of evidence that consist of observational studies (excluding prospective cohort studies) will assume an initial level of confidence of "LOW". The Committee agreed that the certainty of evidence was 'low' due to serious inconsistency, indirectness and imprecision.	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and e-cigarette uptake/initiation compared with no exposure to e-cigarette advertising via multiple media sources (OR: 1.32; 95% CI: 0.93 – 1.88; 2 studies).
2.3	E-cigarette uptake/initiation	Adolescents – never smokers/e-cig users	Social media advertising - exposure	Social media advertising – no exposure	Moderate	Moderate	n=4/6	-	-	Not applicable	Cohort	There is moderate certainty of the evidence that e-cigarette advertising via social media among adolescents likely results in an increase in e-cigarette uptake/initiation compared with no exposure to e-cigarette advertising via social media (OR: 2.60; 95% CI: 1.56 – 4.35; 2 studies).
2.4	E-cigarette uptake/initiation	Adolescents – never smokers/e-cigarette users	Television advertising - exposure	Television advertising – no exposure	Very low	Very low	n=4/6	-	-	Not applicable	Cohort	The evidence is very uncertain on the effect of e-cigarette advertising via television among adolescents on intentions to use e-cigarettes compared with no exposure to e-cigarette advertising via television (OR: 1.11; 95% CI: 0.80 – 1.55; 2 studies).
E-cigarette ever use												
3.1	E-cigarette ever use	Adolescents and young adults – smoking status not specified	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	Very low	Very low	n=5/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and young adults on e-cigarette ever use (OR: 1.28; 95% CI: 1.08 – 1.53; 3 studies).
3.2	E-cigarette ever use	Adolescents and young adults – smoking status not specified	Multiple media sources – (greater) exposure	Multiple media sources – no exposure	Very low	Very low	n=6/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and young adults on e-cigarette ever user compared with no exposure to e-cigarette advertising via multiple media sources (OR: 1.22; 95% CI: 1.08 – 1.39; 4 studies)
												Overall, the evidence is very uncertain about the effect of e-cigarette advertising among adolescents and young adults on e-cigarette ever use.

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
Current e-cigarette use												
4.1	Current e-cigarette use	Adolescents – smoking status not specified	Internet advertising - exposure	Internet advertising – no exposure	Low	Low	n=5/6	-	-	Not applicable	Cross-sectional	There is low certainty evidence that e-cigarette advertising via the internet among adolescents may result in a slight increase in the likelihood of being a current e-cigarette user compared with no exposure to e-cigarette advertising via the internet (OR 1.59; 95% CI: 1.44 – 1.75; 2 studies).
4.2	Current e-cigarette use	Adolescents and young adults – never smokers/e-cigs users and current smokers/users	Multiple media sources – exposure	Multiple media sources – no exposure	Very low	Very low	n=6/6	-	-	Not applicable	Cohort	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and young adults on current e-cigarette use compared with no exposure to e-cigarette advertising via multiple media sources (OR 0.99; 95% CI: 0.83 – 1.18; 3 studies).
4.3	Current e-cigarette use	Adolescents and young adults - smoking status not specified	Multiple media sources (< 3 sources) – exposure sometimes/most of the time/always	Multiple media sources (<3 sources) – never/rarely exposed	Low	Low	n=5/6	-	-	Not applicable	Cross-sectional	There is low certainty evidence that e-cigarette advertising via multiple media sources among adolescents and young adults may result in little to no difference in being a current e-cigarette user compared with no/rare exposure to e-cigarette advertising via multiple media sources (OR 1.28; 95% CI: 1.18 – 1.39; 5 studies).
4.4	Current e-cigarette use	Adolescents and young adults – smoking status not specified	Multiple media sources (n=2-3 sources) – exposure sometimes/most of the time/always	Multiple media sources (n=2-3 sources) – never/rarely exposed	High	Very low	n=6/6	-	-	The Committee agreed that bodies of evidence that consist of observational studies (excluding prospective cohort studies) will assume an initial level of confidence of "LOW". The Committee agreed that the certainty of evidence was 'very low' due to serious risk of bias and indirectness.	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and young adults on current e-cigarette use compared with no/rare exposure to e-cigarette advertising via multiple media sources (OR 2.11; 95% CI: 1.77 – 2.52; 3 studies).
4.5	Current e-cigarette use	Adolescents and young adults – smoking status not specified	Multiple media sources – exposure sometimes/most of the time/always	Multiple media sources – never/rarely exposed	Not specified for secondary outcomes	Very low	n=4/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents on current e-cigarette use compared with no/rare exposure to e-cigarette advertising via multiple media sources (OR 1.30; 95% CI: 1.13 – 1.50; 6 studies).

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
4.6	Current e-cigarette use	Adolescents – smoking status not specified	Retail store advertising - exposure	Retail store advertising – no exposure	Very low	Very low	n=6/6	-	-	Not applicable	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via retail stores among adolescents on current e-cigarette use compared with no exposure to e-cigarette advertising via retail stores (OR 1.48; 95% CI: 1.08 – 2.03; 2 studies).
4.7	Current e-cigarette use	Adolescents – smoking status not specified	Print media advertising - exposure	Print media advertising – no exposure	Moderate	Very low	n=4/6	-	-	The Committee agreed that bodies of evidence that consist of observational studies (excluding prospective cohort studies) will assume an initial level of confidence of "LOW". The Committee agreed that the certainty of evidence was 'very low' due to serious indirectness.	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via print media among adolescents on current e-cigarette use compared with no exposure to e-cigarette advertising via print media (OR 1.33; 95% CI: 1.19 – 1.48; 2 studies).
Combustible cigarette ever use												
5.1	Combustible cigarette ever use	Adolescents and young adults – smoking status not specified	Multiple media sources – exposure	Multiple media sources – no exposure	Low	Very low	n=5/6	-	-	The Committee agreed that bodies of evidence that consist of prospective cohort studies will assume an initial level of confidence of "MODERATE". The Committee agreed that the certainty of evidence was 'low' due to serious risk of bias and indirectness.	Cross-sectional	The evidence is very uncertain about the effect of e-cigarette advertising via multiple media sources among adolescents and young adults on combustible cigarette ever use compared with no exposure to e-cigarette advertising via multiple media sources (OR: 1.49; 95% CI: 1.19 – 1.87; 2 studies).
												Overall, the evidence is very uncertain about the effect of e-cigarette advertising among adolescents and young adults on combustible cigarette ever use.

PICO ref.#	Outcome	Population group	Intervention/exposure	Comparator	Certainty of evidence						Study type	Final evidence statement
					Evidence review	Survey 3a (pooled measures)	Agreement with Survey 3a*	Survey 3b (single studies)	Agreement with Survey 3b*	Rationale for differing certainty of evidence		
Current combustible cigarette use												
6.1	Current combustible cigarette use	Adolescents–smoking status not specified	Retail store advertising – exposure sometimes/most of the time/always	Retail store advertising – never/rarely exposed	Moderate	Low	n=5/6	-	-	The Committee agreed that bodies of evidence that consist of observational studies (excluding prospective cohort studies) will assume an initial level of confidence of "LOW". The Committee agreed that the certainty of evidence was 'very low' due to serious risk of bias and indirectness.	Cohort	There is low certainty evidence that e-cigarette advertising via retail stores among adolescents may result in a slight increase in current combustible cigarette use compared with no/rare exposure to e-cigarette advertising via retail stores (OR 1.69; 95% CI: 1.06 – 2.68; 2 studies).
												Overall, the evidence suggests that e-cigarette advertising among adolescents may result in a slight increase in current combustible cigarette use.
Theme 1: exposure to e-cigarette advertising results in changed perceptions												
Theme 1	Exposure to e-cigarette advertising occurred both actively and passively, resulting in changed perceptions of the risk profile of e-cigarettes	-	E-cigarette advertising (type not specified)	-	Moderate	Moderate	n=6/6	-	-	Not applicable	Qualitative studies	There is moderate certainty evidence that exposure to e-cigarette advertising is likely to be perceived to result in changed beliefs/attitudes of the risk profiles of e-cigarettes (no pooled measures of effect provided; 6 studies).
Theme 2: strategies to enhance the appeal of e-cigarettes are effective												
Theme 2	Strategies used to enhance the appeal and believability of advertisements are effective in influencing perceptions	-	E-cigarette advertising (type not specified)	-	Moderate	Moderate	n=6/6	-	-	Not applicable	Qualitative studies	There is moderate certainty evidence that exposure to high-appeal/convincing e-cigarette advertising is likely to be perceived to result in changed beliefs/attitudes of e-cigarette appeal (no pooled measures of effect provided; 5 studies).
Theme 3: exposure to individuals doing 'vape tricks'												
Theme 3	Exposure to individuals doing 'vape tricks' on social media	-	Social media	-	Moderate	Low	n=5/6	-	-	Not applicable	Qualitative studies	There is low certainty evidence that exposure to individuals doing 'vape tricks' on social media may be perceived to result in an increase in beliefs in that using e-cigarettes are 'trendy', 'cool' and 'fun' (no pooled measures of effect provided; 3 studies).

PICO reference number is unique to each table and may not be consistent across various documents.
* proportion of survey respondents that agreed to the certainty of evidence statement as presented in Survey 3a or 3b.
** as per Appendix A of the Evidence to Decision report, 3/6 respondents thought the certainty of evidence should be very low; 2/6 respondents thought that the certainty of evidence should be low and 1/6 respondents thought the certainty of evidence should be moderate. We have used 'low certainty of evidence' to inform the evidence statement.

Evidence statements: e-cigarettes and health outcomes

Survey 4 had a 60% response rate (completed survey; n=6 out of 10 Committee members). One additional (1) respondent had a partially completed survey; responses were included where available.

Table 3: Summary of certainty of evidence assessments by outcome/exposure and evidence statements

PICO ref.#	Outcome	Population group	Intervention/ exposure	Comparator	Certainty of evidence			Study types ^	Final evidence statement
					Evidence review	Survey 4	Agreement with Survey 4*		
1	Dependence and abuse liability								
1.1	Dependence on e-cigarettes	Non-smokers	E-cigarette use	-	Substantial evidence/ high confidence	Substantial evidence/ high certainty	n=6/ 7	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use among non-smokers results in increased dependence on e-cigarettes.
1.2	Dependence on e-cigarettes	Smokers	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 7	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use among smokers may result in increased dependence on e-cigarettes. Evidence also suggests that e-cigarette use among smokers may have lower abuse liability than combustible cigarettes but may have a higher abuse liability than NRTs.
1.3	Abuse liability risk	Smokers	Flavour and nicotine concentration variations	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=7/ 7	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette flavour and nicotine concentration variations among smokers on abuse liability risk.
								Overall studies examined for this outcome 13 RCTs, 1 Cohort Study, 18 NRIS, 20 Cross-sectional survey	
2	Cardiovascular health outcomes								
2.1	Clinical cardiovascular disease outcomes (for example, myocardial infarction, stroke or cardiovascular mortality)	-	E-cigarette use	-	No available evidence	No available evidence	n=5/ 7	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and clinical cardiovascular disease outcomes (for example, myocardial infarction, stroke or cardiovascular mortality) was identified to-date.
2.2	Subclinical atherosclerosis-related outcomes (for example, carotid intima-media thickness and coronary artery calcification)	-	E-cigarette use	-	No available evidence	No available evidence	n=5/ 7	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and subclinical atherosclerosis related outcomes (for example, carotid intima-media thickness and coronary artery calcification) was identified to-date.
2.3	Other cardiovascular outcomes (increased blood pressure, heart rate, autonomic control and arterial stiffness; reduced endothelial function, hand microcirculation and cardiac function/ geometry; and cardiac device interference)	Non-smokers	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=5/ 7	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among smokers on 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.

PICO ref.#	Outcome	Population group	Intervention/ exposure	Comparator	Certainty of evidence			Study types ^	Final evidence statement
					Evidence review	Survey 4	Agreement with Survey 4*		
2.4	Increased heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness acutely after use	Smokers	E-cigarette use	-	Moderate evidence/ moderate confidence	Moderate evidence/ moderate certainty	n=7/ 7	Could not be determined for each outcome/ exposure	There is moderate certainty evidence that e-cigarette use among smokers likely results in increases in heart rate, systolic blood pressure, diastolic blood pressure and arterial stiffness, shortly after use.
2.5	Increased endothelial dysfunction	Smokers	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=7/ 7	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use among smokers may result in increases to endothelial dysfunction, and that long term e-cigarette use after switching from combustible cigarette smoking may result in decreases to blood pressure.
2.6	Decreased blood pressure after long-term use	Smokers after switching from combustible smoking	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=7/ 7	Could not be determined for each outcome/ exposure	There is low certainty evidence that long term e-cigarette use among smokers after switching from combustible cigarette smoking may result in decreases to blood pressure.
								Overall studies examined for this outcome 1 Meta-analysis, 11 RCTs, 1 Cohort Study, 6 NRIS, 8 Cross-sectional survey, 1 Case report.	
3	Cancer								
3.1	Invasive cancer risk	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and invasive cancer risk was identified to-date.
3.2	Pre-cancer/ subclinical cancer outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and pre-cancer/ subclinical cancer outcomes was identified to-date.
	Sleep								
3.3	Clinical sleep outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and clinical sleep outcomes was identified to-date.
	Wound healing								
3.4	Clinical or subclinical wound healing outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and clinical or subclinical wound healing outcomes was identified to-date.
	Endocrine outcomes								
3.5	Clinical and subclinical endocrine outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and clinical or subclinical endocrine outcomes was identified to-date.
	Allergic diseases								
3.6	Allergic diseases	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and allergic reactions was identified to-date.
	Haematological outcomes								
3.7	Haematological outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and haematological outcomes was identified to-date.
4	Respiratory disease								
4.1	Lung injury (EVALI)	Smokers & non-smokers	E-cigarette use	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use among smokers and non-smokers results in lung injury (EVALI).
4.2	Other clinical respiratory outcomes (asthma, bronchitis and COPD)	Smokers	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among smokers and other clinical respiratory outcomes, including asthma, bronchitis and COPD in smokers.
4.3	Other clinical respiratory outcomes (asthma, bronchitis and COPD)	Non-smokers	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use among non-smokers and other clinical respiratory outcomes (asthma, bronchitis and COPD) was identified to-date.

PICO ref.#	Outcome	Population group	Intervention/ exposure	Comparator	Certainty of evidence			Study types ^	Final evidence statement
					Evidence review	Survey 4	Agreement with Survey 4*		
4.4	Reduction in respiratory exacerbations	Adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use e-cigarettes	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among adult healthy, asthmatic and COPD smokers who switch to exclusive or dual-use e-cigarettes and respiratory exacerbations and disease progression.
4.5	Decrease spirometry parameters up to 25 minutes post exposure	Non-smokers	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use among non-smokers may result in decreased spirometry parameters up to 25 minutes post exposure.
4.6	Decrease spirometry parameters up to 25 minutes post exposure	Smokers	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among smokers and decreases spirometry parameters up to 25 minutes post exposure.
4.7	Spirometry parameters affected 30 minutes to two hours after exposure	Smokers & non-smokers	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use among smokers and non-smokers may result in effects to spirometry parameters 30 minutes to two hours after exposure.
4.8	Increases respiratory resistance and impedance up to 30 minutes post exposure	Healthy & asthmatic smokers	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use among healthy and asthmatic smokers may result in increases in respiratory resistance and impedance in up to 30 minutes post exposure.
4.9	Exhaled breath outcomes	Smokers & non-smokers (healthy and asthmatic)	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among healthy and asthmatic smokers and non-smokers and exhaled breath outcomes.
4.10	Other respiratory measures (sinonasal symptoms, airway hyper responsiveness)	Smokers	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among smokers and other respiratory measures (sinonasal symptoms, airway hyper responsiveness).
4.11	Other respiratory measures (sinonasal symptoms, airway hyper responsiveness)	Non-smokers	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use among non-smokers and other respiratory measures (sinonasal symptoms, airway hyper responsiveness) was identified to-date.
								Overall studies examined for this outcome 9 RCTs, 5 Cohort Studies, 5 NRIS, 18 Surveillance Reports, 21 Cross-sectional Surveys, 11 Case Series, 26 Case Reports	
5	Oral health								
5.1	Clinical or intermediate/ subclinical oral health outcomes	Exclusive e-cigarette users	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use among exclusive e-cigarette users and clinical or intermediate/ subclinical oral health outcomes was identified to-date.
5.2	Reduced plaque, gingival and papillary bleeding	Smokers that switched to e-cigarette use	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among smokers and reduced plaque, gingival and papillary bleeding.

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					Evidence review	Survey 4	Agreement with Survey 4*		
5.3	Increased gum disease, bone loss around the teeth and any periodontal disease	Exclusive e-cigarette users, dual users, and non-smokers (never & former smokers)	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among populations including exclusive e-cigarette users, dual users, and non-smokers (never and former smokers) and increased gum disease, bone loss around the teeth and any periodontal disease.
								Overall studies examined for this outcome 2 Cohort Studies, 2 NRIS, 19 Cross-sectional Surveys, 1 Case Report	
6	Developmental and reproductive effects								
6.1	Development	Fetal, children or adolescents	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No available evidence from human epidemiological or clinical trials on the effect of e-cigarette use on development in children or adolescents was identified to-date.
6.2	Adverse fetal and pregnancy outcomes (low birth weight, preterm birth, low Apgar score and small-for-gestational-age)	Exclusive e-cigarette users or dual users	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use among exclusive e-cigarette users and dual users and adverse fetal and pregnancy outcomes, such as low birth weight, preterm birth, low Apgar score and small-for-gestational-age.
6.3	Other reproductive outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No available evidence from human epidemiological or clinical trials on the effect of e-cigarette use and other reproductive outcomes was identified to-date.
								Overall studies examined for this outcome 2 Cohort Studies, 1 Cross-sectional Survey	
7	Burns and injuries								
7.1	Burns and injuries	-	E-cigarette use	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarettes results in burns and injuries, which can be severe and can result in death.
								Overall studies examined for this outcome 12 Surveillance reports, 19 Case Series, 16 Case Reports	
8	Poisoning								
8.1	Poisoning	-	Intentional or accidental exposure to nicotine e-liquids	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that intentional or accidental exposure to nicotine e-liquids results in poisoning, which can be severe and can result in death.
8.2	Nicotine toxicity	-	E-cigarette use	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use results in nicotine toxicity.
								Overall studies examined for this outcome 25 Surveillance Reports, 4 Case Series, 23 Case Reports	
9	Mental health effects								
9.1	Clinical mental health outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No available evidence from human epidemiological or clinical trials as to how e-cigarettes use affects clinical mental health outcomes was identified to-date.
9.2	Depressive symptoms	-	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use and depressive symptoms.

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					Evidence review	Survey 4	Agreement with Survey 4*		
9.3	Other mental health measures	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No available evidence from human epidemiological or clinical trials regarding e-cigarette use and their effects on other mental health measures was identified to-date.
								Overall studies examined for this outcome 1 Cohort Study, 8 Cross-sectional Surveys	
10	Environmental hazards with health implications								
10.1	Increased airborne particulate matter in indoor environments	-	E-cigarette use	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use results in increased airborne particulate matter in indoor environments.
10.2	Concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces.	-	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use may result in increased concentrations of airborne nicotine and of nicotine and cotinine on indoor surfaces.
10.3	Increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls.	-	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use and increased air levels of carbon dioxide, carbon monoxide, propylene glycol, volatile organic compounds and carbonyls.
10.4	Fires and environmental waste	-	E-cigarette use	-	Substantial evidence/ high confidence	Substantial evidence/ high certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use results in fires and environmental waste.
10.5	Extent that e-cigarette related environmental hazards present a hazard to human health	-	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	m=5/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use and the extent that e-cigarette related environmental hazards present a hazard to human health.
								Overall studies examined for this outcome 17 NRIS, 2 Surveillance Reports, 5 Case Series	
11	Neurological outcomes								
11.1	Seizures	-	E-cigarette use	-	Conclusive evidence/ high certainty	Conclusive evidence/ high certainty	n=5/ 6	Could not be determined for each outcome/ exposure	There is high certainty evidence that e-cigarette use results in seizures.
11.2	Nerve damage via explosions	-	E-cigarette use	-	Limited evidence/ low confidence	Limited evidence/ low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is low certainty evidence that e-cigarette use may result in nerve damage via injuries due to e-cigarette explosions.
11.3	Other clinical neurological outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and how it affects the risk of other clinical neurological outcomes was identified to-date.
								Overall studies examined for this outcome 3 Surveillance Reports, 2 Case Series, 7 Case Reports	

PICO ref.#	Outcome	Population group	Intervention/ exposure	Comparator	Certainty of evidence			Study types ^	Final evidence statement
					Evidence review	Survey 4	Agreement with Survey 4*		
12	Less serious adverse events								
12.1	Less serious adverse events (for example, throat irritation, cough, dizziness, headache and nausea)	-	Nicotine e-cigarette use	-	Moderate evidence/ moderate confidence	Moderate evidence/ moderate certainty	n=6/ 6	Could not be determined for each outcome/ exposure	There is moderate certainty of evidence that nicotine e-cigarette use likely results in less serious adverse events – such as throat irritation, cough, dizziness, headache and nausea.
								Overall studies examined for this outcome 11 RCTs, 2 Cohort Studies, 2 NRIS, 1 Surveillance Report, 3 Cross-sectional surveys	
13	Optical health								
13.1	Clinical optical outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and relation to clinical optical outcomes was identified to-date.
13.2	Corneal epithelial thickness or pre-corneal tear film stability	-	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use and corneal epithelial thickness or pre-corneal tear film stability.
13.3	Other optical outcomes	-	E-cigarette use	-	No available evidence	No available evidence	n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and other optical outcomes was identified to-date.
								Overall studies examined for this outcome 1 NRIS, 1 Cross-sectional Survey	
14	Olfactory outcomes								
14.1	Clinical olfactory outcomes	-	E-cigarette use	-	No available evidence	No available evidence	100% n=6/ 6	Not applicable	No evidence from human epidemiological or clinical trials on e-cigarette use and clinical olfactory outcomes was identified to date.
14.2	Olfactory measures	-	E-cigarette use	-	Insufficient evidence/ very low confidence	Insufficient evidence/ very low certainty	100% n=6/ 6	Could not be determined for each outcome/ exposure	The evidence is very uncertain about the effect of e-cigarette use and olfactory measures.
								Overall studies examined for this outcome 1 Cross-sectional Survey	

PICO reference number is unique to each table and may not be consistent across various documents.
*proportion of survey respondents that agreed to the certainty of evidence statement as presented in Survey 4.
^ Some studies were identified by the evidence reviewer, however if the conclusion was that there is no available evidence then 'not applicable' was written in the study type. For study eligibility criteria please refer to the evidence review.

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