

# Health consequences of electronic cigarettes

Protocol for an umbrella review

# Summary

Electronic cigarettes (e-cigarettes), both with or without nicotine, have increased in popularity in many countries. There is wide variation in product types and contents. The products are sold under the assumption that e-cigarettes may be less harmful to health than highly unhealthy conventional tobacco cigarettes. The need to systematically review existing evidence on consequences to human health from e-cigarettes is high and increasing.

On commission from the Ministry of Health and Care Services in Norway we will systematically evaluate health consequences of use of and exposure to e-cigarette aerosols (secondhand exposure). The evaluation will be based on scientific methods for collection and assessments of systematic reviews of health consequences associated with use of e-cigarettes.

In order to identify relevant reviews, we will conduct a systematic search for literature. Titles and abstracts will be considered according to the inclusion and exclusion criteria. References will be screened by two researchers independently, first by title and abstract and subsequently in full text, for inclusion and exclusion.

The quality of included systematic reviews will be assessed using AMSTAR-2. For each health outcome, we will use the most up to date systematic review of high quality to summarise health consequences. If the review has not graded the quality of the evidence, then we will use the GRADE approach to do so.

**Title:** Health consequences of electronic cigarettes: Protocol for an umbrella review

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**Commissioner:** Ministry of Health and Care Services in Norway

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**Commissioned date:** September 2021

**Due date:** 01.03.2022

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# Sammendrag

Elektroniske sigaretter (e-sigaretter), både med og uten nikotin, har blitt populære i mange land. Det er en stor variasjon i produkttyper og innhold. Produktene selges med en antakelse om at e-sigaretter er mindre helseskadelige enn svært helseskadelige konvensjonelle sigaretter. Det er behov for å fremskaffe en systematisk oversikt over tilgjengelig kunnskap om hvilke konsekvenser e-sigaretter har på helsen.

På oppdrag fra Helse- og omsorgsdepartementet skal vi vurdere helsekonsekvenser av bruk av e-sigaretter og eksponering for e-sigaretter i omgivelsene (annenhandts eksponering). Denne vurderingen skal baseres på en vitenskapelig utført sammenfatning og vurdering av systematiske oversikter om helsekonsekvensene av e-sigaretter.

For å finne relevante systematiske oversikter skal vi søke systematisk i litteraturredatabaser. Tittel og sammendrag vil bli vurdert etter forhåndsdefinerte inklusjons- og eksklusjonskriterier. Referansene vurderes ved at to forskere parvis og uavhengig av hverandre først vurderer titler og sammendrag og så fulltekstversjon for inklusjon og eksklusjon. Vi vil vurdere kvaliteten på de inkluderte oversiktene ved hjelp av AMSTAR-2. For hvert endepunkt vil vi bruke den mest oppdaterte oversikten av høy kvalitet til å videreformidle helsekonsekvensene. Dersom oversikten ikke har vurdert kvaliteten på dokumentasjonen så vil vi gjøre dette selv ved bruk av GRADE metoden.

**Tittel:**

Helsekonsekvenser av elektroniske sigaretter: prosjektplan for en paraplyoversikt

**Oppdragsgiver:**

Helse- og omsorgsdepartementet

**Bestillingsdato:**

september 2021

**Leveringsfrist:**

01.03.2022

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# Commission

The Ministry of Health and Care Services requested the Norwegian Institute of Public Health (NIPH) to elucidate the health effects of e-cigarettes, in a two-part assignment. The first part of the assignment was to perform a systematic literature search and prepare an interactive evidence and gap map of research on health effects of electronic cigarettes (e-cigarettes) use. The research map is completed and published (Valen et al., 2021).

The second part of the assignment was specified in September 2021 and is to perform an update of the literature search, and to evaluate possible health effects linked to the use of e-cigarettes or secondhand exposure. This part will be based on a scientific evaluation of the systematic reviews found.

The systematic literature search should be restricted to studies addressing health effects and not include other e-cigarette related issues such as harm reduction (here the possibility that the use of e-cigarettes compared with other tobacco products may be less harmful) and "gateway" (here the possibility that use of e-cigarettes leads to use of other tobacco or nicotine containing products) or the use of e-cigarettes in smoking cessation.

In agreement with the established policy of leading scientific journals, research funded by or otherwise linked to the tobacco industry should not be included. Otherwise, NIPH is free to organize the work as they find appropriate, including consultation with any external expertise.

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# Background

Electronic cigarettes (e-cigarettes) consist of a heating element associated with a battery and a cartridge containing a liquid (e-cigarette liquid). When heated, the e-cigarette liquid will form an aerosol (vapour) meant to be inhaled through a mouthpiece. E-cigarettes can be disposable, rechargeable with a cartridge, or manually refillable with e-cigarette liquid.

The e-cigarette liquid can contain nicotine or be nicotine free. In addition, the e-liquid usually contains a mixture of propylene glycol (PG), vegetable glycerine (VG), and various flavourings. The available number of these flavours/combination of flavours is exceedingly high. Heating of the e-liquid can lead to thermal decomposition of these constituents and/or formation of new compounds, depending on the temperature, chemical composition and duration of the heating. The composition of decomposed products and new compounds may be unpredictable, and the products may possess altered toxicity compared with their parent compounds. Other constituents found in aerosols including metals and silicate particles may add to the toxicity of the inhaled vapour (SCHEER, 2020).

The harmful potential of nicotine has been documented from studies in cell cultures, animals and, although less, in humans (US Surgeon General, 2014). The health risks associated with *inhalation* of e-liquid aerosol with or without nicotine and containing PG/VG and flavours have not been thoroughly elucidated in human studies. However, numerous *in-vitro*- and animal studies have been performed to elucidate the potential health consequences these inhalable constituents confer. Several of these studies report cellular effects that may have impact on airways, inflammation, impairment of cardiovascular function and toxicity. In addition, some of the compounds identified in aerosol from e-liquid are known or potential carcinogens.

The composition of the inhaled vapour is affected by the e-cigarette device and e-liquid as well as the vaping pattern which all affect the dose of toxicants the user and people in close proximity are exposed to. Any adverse outcomes will also depend on user/exposed specific (genetic) and environmental factors that may predispose for health effects (NASEM, 2018; SCHEER 2020). Thus, a more precise evaluation of the health risks linked to e-cigarettes use is complicated due to the large variation of products on the market and the heterogeneity of users (e.g. time of use, age of user, comorbidity). Furthermore, the potential long-term effects of e-cigarette use have so far only been scarcely investigated.

There is an increasing number of studies addressing adverse impacts of e-cigarettes on human health, such as e-cigarette - vaping associated lung injury (EVALI) often related to use of e-liquids containing THC, poisoning after ingestion of nicotine containing e-liquid by infants as well as explosions and burns.

It should also be noted that e-cigarettes may be used for vaping other liquids or additives that may be illegal or produced for other purposes, and thus not provided commercially from an e-cigarette producer. However, such unauthorised use is beyond the scope of this report.

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### **Why it is important to conduct this umbrella review**

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Since the introduction of e-cigarettes on the market, a development and diversification of both the e-cigarette and e-liquids has followed. The amount of scientific literature on health effects of e-cigarettes is increasing rapidly. Thus, there is a need for an up-to-date overview of the available scientific information on health consequences of e-cigarettes to secure evidence based information and regulations of e-cigarettes. As e-cigarettes are introduced to new markets, updated health risk assessments associated with their use or exposure become more important.

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### **Aims**

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The aim of this project is to conduct an umbrella review (systematic review of systematic reviews) of the health effects from use of or exposure to electronic cigarettes.

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# Methods

We will prepare this umbrella review (systematic review of systematic reviews) in accordance with the NIPH methods book (Folkehelseinstituttet. Slik oppsummerer vi forskning. Metodebok) and the Cochrane Hand book (Higgins et al., 2021).

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## Inclusion criteria

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We will use the following inclusion criteria:

<b>Population</b>	Human and animal
<b>Intervention or exposure</b>	All types of electronic cigarettes and additives
<b>Comparison</b>	No restrictions: smoking, smokeless tobacco, or no use of tobacco product allowed as comparison
<b>Outcomes</b>	All health outcomes as a result of the use of e-cigarettes
<b>Study design</b>	Systematic review (with a description of literature search, clear inclusion criteria and risk of bias assessment of included studies)
<b>Publication time</b>	No restrictions
<b>Country/ context</b>	No restrictions
<b>Language</b>	Danish, English, Norwegian, Swedish

## Exclusion criteria:

- Research funded by or otherwise linked to the tobacco industry
- Harm reduction publications without evidence of health outcomes
- Studies that only describe or discuss the pattern of use of tobacco products
- Primarily addiction focused research
- Reviews and discussion papers without systematic literature search, clear inclusion criteria and risk of bias assessment of the included studies

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## Literature search

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Research librarian Miriam Bakkeli will update the systematic literature search that she developed in collaboration with the project group and conducted in connection with the interactive evidence and gap map on the health effects of e-cigarettes (Valen et al., 2021).

The strategy was peer reviewed by another research librarian before she conducted the searches first time. The following databases will be searched:

- Ovid MEDLINE
- Embase
- PsycInfo
- Web of Science
- Cochrane Database of Systematic Reviews

In addition we will check the web sites of relevant institutions and organisations such as Statens Beredning för Medicinsk och Sosial Utvärdering (SBU; <https://www.sbu.se/>), National Academies of Sciences, Engineering, and Medicine (NASEM; <https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes>), Scientific Committee on Health, Environmental and Emerging Risks (SCHEER; [https://ec.europa.eu/health/scientific\\_committees/scheer\\_en](https://ec.europa.eu/health/scientific_committees/scheer_en)), National Institute for Health and Care Excellence (NICE; <https://www.nice.org.uk/>), Public Health England (PHE, currently UK Health Security Agency) and Office for Health Improvement and Disparities(<https://www.gov.uk/government/organisations/office-for-health-improvement-and-disparities>).

The complete and updated search strategy will be shown in full in the completed report.

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## **Selection of studies**

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Two authors from the working group (RB, HV, BCB, JAH, GEV and TKG) will read through and assessed each of the references identified in the literature searches. Relevant references will be selected on the basis of our inclusion and exclusion criteria. The first selection will be based on the title and abstract, and the second selection on the full-text versions of the publications. Any disagreements will be resolved through discussion or contact with another researcher in the team. We will use the software EPPI Reviewer 4 for the study selection.

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## **Assessing the quality of systematic reviews**

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We will use AMSTAR-2 to assess the quality of the included systematic reviews (Shea et al., 2017). Two authors from the working group (VU, HV, RB, BCB and GEV) will assess the quality for each of the included systematic reviews. Any disagreements will be resolved through discussion or contact with another researcher in the team.

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## **Data collection and grading**

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For each health outcome, we will use the most up to date systematic review of high quality to summarise health consequences.



One author from the author working group (RB, HV, BCB, JAH, GEV and TKG) will collect data from the systematic review, and another person from the same author group will check that the correct information has been collected correctly. We will collect information on:

- the full reference
- the date of the literature search
- number and type of studies included, when and where it was conducted
- number and characteristics of participants in the studies
- type and content of e-cigarettes used
- type and content of comparison
- outcomes measured
- results, including grading results if conducted

Where the systematic reviews have graded their confidence in the evidence, we will look to their assessments. When the evidence is not already graded, then we will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess our confidence in the quality of the documentation (Balslem et al., 2011).

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## **Peer review of project plan and report**

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The project plan will only undergo an internal peer review. The working group consists of professionals with expertise in medicine, dentistry and toxicology as well as health researchers, specializing in a number of disciplines including causal cancer research, pregnancy outcomes, cardiovascular disease, respiratory diseases and lung injuries, neurological diseases, environmental and occupational diseases as well as psychiatry. Others have their expertise in systematic reviews, meta-analysis and general study design. The report will undergo peer review by both internal and external peer reviewers.

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## **Related projects at the NIPH**

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NIPH 2021. Valen H, Vist GE, Becher R, Brinchmann BC, Holme JA, Grimsrud TK, Ørjasæter Elvsaa I-K, Underland V, Bakkeli M, Alexander J. Health risks associated with the use of electronic cigarettes: an interactive research map. [Helseerisiko ved bruk av elektroniske sigaretter: et interaktivt forskningskart] –2021. Oslo: Norwegian Institute of Public Health, 2021.

[https://www.fhi.no/contentassets/4b2f92c4a2034eb5a7513e5a371c9524/20210901\\_e-cig-report.pdf](https://www.fhi.no/contentassets/4b2f92c4a2034eb5a7513e5a371c9524/20210901_e-cig-report.pdf)

NIPH, 2019. Oppsummering av og redegjørelse for det pågående sykdomsutbruddet i USA knyttet til bruk av elektroniske sigaretter. (Summary of and account of the ongoing disease outbreak in the United States related to the use of electronic cigarettes).

[https://www.fhi.no/globalassets/dokumenterfiler/notater/2019/notat\\_sykdomsutbruddet-i-usa-knyttet-til-e-sigarettersykdomsutbrudd.pdf](https://www.fhi.no/globalassets/dokumenterfiler/notater/2019/notat_sykdomsutbruddet-i-usa-knyttet-til-e-sigarettersykdomsutbrudd.pdf)

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NASEM. National Academies of Sciences, Engineering, and Medicine. *Public Health Consequences of E-Cigarettes*. Washington, DC, The National Academies Press, 2018. [https://www.ncbi.nlm.nih.gov/books/NBK507171/pdf/Bookshelf\\_NBK507171.pdf](https://www.ncbi.nlm.nih.gov/books/NBK507171/pdf/Bookshelf_NBK507171.pdf)

Valen H, Vist GE, Becher R, Brinchmann BC, Holme JA, Grimsrud TK, Ørjasæter Elvsaas I-K, Underland V, Bakkeli M, Alexander J. Health risks associated with the use of electronic cigarettes: an interactive research map. [Helserisiko ved bruk av elektroniske sigaretter: et interaktivt forskningskart] –2021. Oslo: Norwegian Institute of Public Health, 2021. [https://www.fhi.no/contentassets/4b2f92c4a2034eb5a7513e5a371c9524/20210901\\_e-cig-report.pdf](https://www.fhi.no/contentassets/4b2f92c4a2034eb5a7513e5a371c9524/20210901_e-cig-report.pdf)

SCHEER 2020. Scientific Committee on Health, Environmental and Emerging Risks. Preliminary Opinion on electronic cigarettes. [https://ec.europa.eu/health/sites/health/files/scientific\\_committees/scheer/docs/scheer\\_o\\_017.pdf](https://ec.europa.eu/health/sites/health/files/scientific_committees/scheer/docs/scheer_o_017.pdf)

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US Surgeon General, 2014. *The health consequences of smoking – 50 years of progress: a report of the Surgeon General*. – Atlanta, GA. : U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014. [https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf\\_NBK179276.pdf](https://www.ncbi.nlm.nih.gov/books/NBK179276/pdf/Bookshelf_NBK179276.pdf)

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<https://www.fhi.no/kk/oppsummert-forskningfor-helsetjenesten/slik-oppsummerer-vi-forskning/>