# Health risks associated with the use of electronic cigarettes

A protocol for an interactive research map

# Summary

Electronic cigarettes, both with and without nicotine, have increased in popularity in many countries. There is a large variation in product types and contents. There is an equally large and increasing need to map existing evidence on potential consequences to human health.

**Project plan for an interactive research map**
The projects main goal is to systematically map existing research on health risks associated with use of electronic cigarettes, and to identify possible research gaps.

An interactive research map will be prepared, which is a systematic and visual presentation of available research on the broad thematic area of health consequences of using electronic cigarettes.

**Title: Health risks associated with the use of electronic cigarettes**

---

Project plan for an interactive research map

---

**Responsible for assignment/commissioned by:**
Ministry of Health and Care Services

---

**Start date:**
16.09.2020.

**End date:**
30.06.2021

---

**Team:**
Rune Becher (teamleader)
Håkon Valen
Bendik Brinchmann
Jørn A. Holme
Gunn E. Vist
Ida-Kristin Ørjasæter Elvsaas
Tom K. Grimsrud
Elisabeth Øya
Miriam Bakkeli (librarian)
Jan Alexander

---

**Reviewers:**
Kjetil Gundro Brurberg,
Head of department, NIPH

**Approved by:**
Johan Øvrevik, Specialised director, NIPH

# Commission

In 2020, the Ministry of Health and Care Services (HOD) requested the Norwegian Institute of Public Health (NIPH) to update and expand the report «Health risks from the use of e-cigarettes» published by the NIPH in 2015 (**1**). The mandate for the assignment of a new report on health risks associated with the use of e-cigarettes was given in June 2020 and was used as a basis for the new report:

The Ministry refers to the NIPH's report "Health risk from the use of e-cigarettes" from 2015. Since then, new products with changes in design and content have been introduced, and the scientific literature on health effects of e-cigarettes has increased significantly. Thus, there is a need for updated information. We also refer to the discussion on the matter at the agency management meeting on 2nd June, 2020. The Ministry gave the NIPH a two-part assignment:

The first part of the assignment will consist of a systematic literature search and subsequent preparation of an interactive map of e-cigarette research. This research map shall include all studies classified by type of publication and topic of the research. Areas where research is lacking (or insufficient) should be identified. This map will be useful for getting an orientation on available research, and will support the further work with systematic overviews of research on e-cigarettes. The map shall exclude issues such as harm reduction and "gateway" (here the possibility that use of e-cigarettes lead to use of other tobacco or nicotine containing products), and the use of e-cigarettes in smoking cessation. Research funded by or otherwise linked to the tobacco industry shall not be included. This in agreement with the established policy of leading scientific journals. Otherwise, NIPH is free to organize the work with the interactive map, as found appropriate, including consultation with any external expertise. The present protocol belong to part one of the assignment. Deadline for part one is 30th June, 2021.

In part two, a health risk assessment of e-cigarette use will be made using standard systematic review methodology of available, relevant research literature. This means that when we summarize health risks in accordance with international standards for systematic reviews, our confidence in the effect estimates is graded using the GRADE method. The health risk assessment will be based on a relevant health issue that HOD will decide on when they have the information presented in the research map at their disposal.

# Background

## Description of existing regulations

The Tobacco Products Directive 2014/40/EU (2) presents rules for manufacture, presentation and sale of tobacco and related products in the EU (2). The background for the revised Tobacco Product Directive was to have the regulations updated and in line with the market, research and international developments in the area. Several new products had been introduced on the market, and new market strategies had been applied. The directive also aimed to improve the functioning of the internal market for tobacco and related products and at the same time focus on the protection of European public health. Article 20 of the TPD introduced for the first time a harmonized and comprehensive regulatory framework for e-cigarettes with the attention to safety, quality, consumer protection and data collection. The directive also set a maximum limit for nicotine content, and included a ban on certain additives (3). With the exception of nicotine, the directive required that member states ensure that only ingredients be used that do not pose a health risk in unheated or heated form. It is, however, not clear what documentation must be provided to show that products and product ingredients do not pose a health risk. Account should be taken of the fact that heating conditions and temperature may affect and change the chemical composition and toxicity of the vapour.

Regulation in the European Union states that manufacturers and importers must register the products with the relevant authorities of the Member States (2 (a)) via the European submission portal, EU-CEG. The registration must include information on ingredients and emissions, toxicological data, information on nicotine doses and uptake, and a description of the equipment and production processes. E-cigarette liquids must not contain more than 20 mg/mL nicotine (2 (b)), tanks and cartridges must not exceed 2 mL and refill containers must not exceed 10 mL (2 (c)). Refill containers and e-cigarettes must also be childproof and tamper-proof, and sold with instructions for use and health warnings (2 (d)). Member States regulate flavours and age limits.

Since e-cigarettes are considered "a new nicotine product" in Norway, they are covered by regulations that ban new tobacco and nicotine products (4). E-cigarettes with nicotine are therefore prohibited to produce, import and sell, and are to be regarded as a tobacco surrogate to be regulated by the tobacco legislation. However, the directive's provisions on e-cigarettes and e-cigarette liquids have been implemented in the Norwegian Tobacco

Damage Act (5), but have not yet been enforced. This follows from the fact that in December 2016, Parliament decided to lift the ban on sale of e-cigarettes with nicotine (6).

The new regulations for e-cigarettes will most likely enter into force in 2021. A registration scheme was adopted which is regulated by TPD. The EU countries started with this regulation in November, 2016, but Norway is waiting for the directive to be incorporated into the EEA agreement. The Norwegian Medicines Agency is given administrative responsibility for supervising the product requirements and the registration scheme. The new regulations set extensive requirements for the content, quality, safety and labelling of all e-cigarettes and refill containers (e-cigarette liquids, e-cigarette juice) both with and without nicotine content.

## Description of and characteristics of e-cigarettes

E-cigarettes vary greatly in design and complexity, and basically contain liquid (e-cigarette liquid, e-cigarette juice) which, when heated, forms an aerosol (vapour) that can be inhaled. The main components of such an evaporator consist of a liquid-filled container or tank for e-liquid, an evaporator unit/heating element, a nozzle, and a battery unit. Other terms such as ENDS (electronic nicotine delivery system) and NVP (nicotine vaping products) are also used.

Early e-cigarettes originated from a product developed and patented in China in 2003. They were launched on the American market in 2006. E-cigarettes can be disposable, rechargeable with a cartridge, or manually refillable from refill containers that contain e-cigarette liquid. Later, several generations of products have been introduced on the market and very few of them look like conventional cigarettes. First-generation e-cigarettes were often imitations (often called cigalikes) ", but larger and more advanced products have appeared later. They may still be shaped like a pen, but larger and cylindrical, and are often referred to as "tank systems" that can contain larger amounts of e-cigarette liquid than earlier models. Third generation e-cigarettes consist of a diverse range of products often termed as "vaping" products. The design has less resemblance to cigarettes, as they may be square or rectangular and may have options for customizing and conversion. These are often referred to as "mods", since the users can change the device or build their own version (3).

The e-cigarette liquid is usually a mixture of propylene glycol, glycerol, and flavourings and may contain nicotine or be nicotine free. Other products may contain a cocktail of vitamins including A, C or D or other ingredients as well as naturally occurring compounds such as amino acids and collagen. The harmful potential of nicotine is well documented in experimental studies in cell studies and animal experiments and to some extent in humans (7). Furthermore, effects of exposure to nicotine in the form of aerosol only may be different from those seen from smoking or the use of oral moist tobacco (snus). Many of the supplementary compounds have been thoroughly evaluated for

potential health risks following oral intake but not by inhalation. The health risk of the inhaled vapour may be affected by chemical composition that is modified by heat source, element temperature, temperature gradient and duration of contact between the element and the e-liquid as well as exposure dose (3; 8). Notably, e-cigarettes may also be used for vaping other liquids or compounds that may be illegal, produced for other purposes (i.e. mixed by the users themselves) and not provided commercially from the e-cigarette producer. .

## Why is it important to make this interactive research map

The Ministry of Health and Care Services wants an overview of available research and evidence about the health effects from use of electronic cigarettes before making decisions about these products in Norway. The interactive research map will be part of the knowledge base for making informed decisions.

There is a rapid development, changes and diversification in product design, equipment and ingredients combined with a continuous stream of new research publications. Thus, any overview of this research field will quickly need updating. It is now six years since the search was conducted for the previous NIPH report on health risks from use of e-cigarettes. Even the NASEM report on the "Public Health Consequences of E-Cigarettes" from 2018 with a search from August, 2017 can benefit from updating (3). The European report currently out for public consultation (8) was based on a literature search in April 2019, although the report does not include a clear description of the methods used for inclusion and evaluation of the scientific literature. In the same report, health consequences were only fully described for cardiovascular diseases.

## Purpose

The purpose of this report is to systematically search for, identify, categorize and present in an interactive map the available research on health risks associated with the use of electronic cigarettes.

# Method

We will prepare an interactive research map of studies on health risks associated with the use of electronic cigarettes. We will proceed in a systematic and scientific way to map existing research on the topic. The research map will provide a systematic and visual overview by providing a graphical representation of areas with many, some or non-existent scientific documentation. The identified research gaps can further indicate where future research may be useful. The research map will visualise what research is available; it will not assess the size of the health risk associated with electronic cigarettes.

We will prepare the research map in accordance with Campbell Collaboration's framework for evidence and gap maps (9).

## Problem statement

The aim of this interactive research map is to systematically search for, identify and categorize available research on health risks from the use of electronic cigarettes.

## Inclusion criteria

The following inclusion criteria will be used:

| | |
|---|---|
| **Populations:** | No restrictions, all human-, animal- and in-vitro studies |
| **Measures:** | All types of electronic cigarettes and additives |
| **Comparison:** | No restrictions, no use of tobacco product, smoking, snuff |
| **Outcomes:** | All health outcomes as a result of the use of electronic cigarettes |
| **Study design:** | No restriction |
| **Population year:** | No restriction |
| **Language:** | Danish, English, Norwegian, Swedish |

All categories will be divided into subcategories, suggested codes are presented in the codebook in Appendix 1. We will pilot the categorisation and may improve on the codes when piloting.

**Exclusion criteria:**

- Research funded by or that otherwise has links 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
- Dependence research
- Discussion papers without primary data or secondary analysis

## Literature search

The project group will, in collaboration with the research librarian Miriam Bakkeli prepare a complete search strategy. We will search in the following databases: Ovid MEDLINE, Embase, PsycInfo, Web of Science and Cochrane Database of Systematic Reviews.

## Selection of studies

Two people will read through and assess each of the references identified in the literature searches. Relevant references are selected on the basis of the inclusion criteria. The selection takes place stepwise, first on the basis of title and summary/abstract, and then full-text versions of the publications. Any disagreements are resolved through discussion or contact with another researcher in the team. We will use the software EPPI Reviewer 4.

## Data collection and presentation

Our framework for categorisation is presented in the codebook presented in Appendix 1. EPPI Reviewer 4 software will be used to code the included studies. At least two people will categorize the selected publications independently of each other. Any disagreements will be resolved by discussion.

The interactive research map will present categories and subcategories, and text and tables will describe these in a report.

## Assessment of the risk of systematic biases and confidence in the results

The research map will provide an overview of the scope and type of research on the health effects of electronic cigarettes. This work does not include assessment of the risk of systematic biases in the included studies, analysis or assessment of confidence in the effect estimates.

## Peer review of project plan and report

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, occupational diseases and psychiatry. Others have their expertise in systematic reviews, meta-analysis and general study design.

The report accompanying the interactive research map will undergo peer review by both internal and external peer reviewers.

## Timeframe

**Start date:** 16.09.2020
**Final date:** 30.06.2021

| ***Stage/partial delivery*** | **Start date** | **Final date** |
|---|---|---|
| *Development of project plan* | 22.09.20 | |
| *Literature search* | December 2020 | December 2020 |
| *Selection of studies* | Jan-Feb 2021 | Jan-Feb 2021 |
| *Data collection* | March 2021 | March-May 2021 |
| *Preliminary report* | May 2021 | May 2021 |
| *Peer review* | June 2021 | June 2021 |
| *Approval* | June 2021 | June 2021 |
| *Submission to client and publication* | | **30.06.2021** |

### Measures in case of delay

The director of Department of air pollution and noise/director of Division of Infection Control and Environmental Health allocate more people or persuades the Ministry of Health to postpone the delivery deadline.

## Deliverables and publication

The project's deliverables will be an NIPH report where the live/interactive research map's categories are presented in tables and text describing the existence of available research. In addition, an interactive research map will be prepared. The interactive research map will be available as an html file, which may be published as a website. The website will show an interactive matrix that illustrates the landscape of evidence on health risks of using electronic cigarettes.

The target group for the report and the interactive research map is the Ministry of Health and Care Services. Both the report and the interactive research map may also be of interest to politicians, decision-makers nationally and locally, research funding agencies, clinicians in the first- and second-line services, researchers and the general population.

The Ministry of Health and Care Services will receive the report and the interactive research map two weeks before they are published on www.fhi.no.

**Keywords:** electronic cigarettes, e-cigarettes, vaping, steaming, research maps

## Related projects/publications/studies at NIPH

NIPH, 2015. Health risks associated with the use of electronic cigarettes. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2015/helserisiko-ved-bruk-av-e-sigaretter-pdf.pdf

NIPH 2019. Health risks from snus use. Norwegian Institute of Public Health. Report 2019, version 2. https://www.fhi.no/globalassets/bilder/rapporter-og-trykksaker/2019/helserisiko-ved-snusbruk-rapport-2019-v2.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_sykdomsut-bruddet-i-usa-knyttet-til-e-sigarettersykdomsutbrudd.pdf

## References

1. NIPH, 2015. Health risks associated with the use of electronic cigarettes. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/2015/helserisiko-ved-bruk-av-e-sigaretter-pdf.pdf

2. EU TPD, 2014. DIRECTIVE 2014/40/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC
https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=OJ%3AJOL_2014_127_R_0001
a: Article 20 (2)
b: Article 20 (3) (b)
c: Article 20 (3) (a)
d: Article 20 (3) (g), (4) (a) and (b)

3. 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

4. https://lovdata.no/dokument/SF/forskrift/1989-10-13-1044, § 2

5. Norwegian Tobacco Damage Act (Lov om vern mot tobakksskader (tobakksskadeloven)). https://lovdata.no/dokument/NL/lov/1973-03-09-14

6. https://www.stortinget.no/no/Saker-og-publikasjoner/Vedtak/Beslutninger/Lovvedtak/2016-2017/vedtak-201617-026/

7. 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

8. SCHEER 2020. Scientific Committee on Health, Environmental and Emerging Risks. Preliminary Opinion on electronic cigarettes. https://ec.europa.eu/health/sites/health/files/scientific_commitees/scheer/docs/scheer_o_017.pdf

9. https://campbellcollaboration.org/evidence-gap-maps.html

# Appendix 1 Code book

| | | |
|---|---|---|
| ***Code book for interactive research maps on health consequences associated with the use of electronic cigarettes*** | | |
| | **Type of publications** | Comments: |
| | Systematic reviews (including HTA) | With search and quality assessment of included studies |
| | Non-systematic review | Literature search but not quality assessment<br>No other codes needed |
| | Randomised Controlled Trials (RCT) | |
| | Non-randomised controlled study | |
| | Prospective study | |
| | Retrospective study | |
| | Case-control study | |
| | Case reports | Follow up is “single time event” |
| | Cross sectional study | Follow up is “no follow up” |
| | Animal studies | |
| | *In vitro* studies | |
| | Model or physical/chemical analysis | |
| | Other | |
| | Comment or editorial for later interest- not shown on map | No other codes needed |
| | | |
| | **Population** | Population and Pattern of product use only for human studies |
| | Human - not reported | |
| | Pregnant and infants | |
| | Children < 16 years | |
| | Adolescents and young adults 16-24 years | |
| | Adults > 25 | |
| | | |
| | **Follow-up time of the cohort** | |
| | Single time event | |
| | < 6 months | |
| | 6 months to <2 years | |
| | >2 years | |
| | No follow up | |
| | | |
| | **Pattern of product use** | |
| | e-cigarette use only | |
| | E-cigarette use (history of other tobacco products not specified) | |
| | Concurrent use of other tobacco product(s) | |
| | e-cigarette second hand exposure | |
| | No previous use of tobacco | |
| | Previous tobacco use | |
| | Not reported | |

| | | |
|---|---|---|
| | Other | |
| | | |
| **Exposure characterisation and assessment (including liquid content)** | | |
| | Liquid content - with nicotine | |
| | Liquid content- with nicotine salts | |
| | Liquid content - without nicotine | |
| | Liquid content - Others additions like flavour, vit E acetate, etc | |
| | Device temperature reported | |
| | External dose: nicotine content, puffing frequency, etc | |
| | Internal dose: Substances levels from vaping measured in blood/urine | |
| | Not given or not reported | |
| | Other | |
| | | |
| **Health consequences** | | |
| | Oral | |
| | | |
| | Airways and pulmonary | |
| | | |
| | Cardiovascular & vascular | |
| | | |
| | Gastro-intestinal (GI) | |
| | | |
| | Central nerve system | |
| | | |
| | Mental health | |
| | | |
| | Cancer | |
| | | |
| | Immune system | |
| | | |
| | Metabolic disorders | |
| | | |
| | Pregnancy | |
| | | |
| | Mortality | |
| | | |
| | Other adverse events | Such as poisoning and burns/ explosions |
| | | |
| | Other biomarkers | |
| | | |
| | Mechanistic and/or in vitro | |
| | | |
| | Sexual health | |
| | | |
| | Kidney and urological tract | |