Work Package 7: Health impact and regulatory implications of e-cigarettes and novel tobacco products

D 7.3:
Report on relevant health risks for novel tobacco products, e-cigarettes

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General summary

Background

Within the scope of the 2nd Joint Action on Tobacco Control (JATC 2) in the European Union, emphasizing the evaluation of health impacts related to novel tobacco products and electronic cigarettes. The assessment encompasses ingredients, additives, devices, and emissions which seek to categorize these products based on their health risk potential. The main objective of the report is to investigate the health risk profiles associated with high-priority substances from electronic cigarettes and heated tobacco products. It builds on a previous JATC2 report from 2022, highlighting key factors contributing to health risks of e-cigarette use, such as substance mixtures, device characteristics, Do It Yourself (DIY) practices, and the aging process which will be explained in the present report. The synthesis of these findings, derived from a literature review, contributes to the development of the present report (D7.3), which specifically focuses on the health risks of electronic cigarettes and heated tobacco products.

Health hazards

A total of 133 high-priority substances, including ingredients and emissions, underwent categorization based on various hazard criteria, including classifications such as human carcinogens, mutagens, reproductive toxicants, endocrine disruptors, toxicity for specific organs upon repeated exposure, respiratory sensitizers, or highly acutely toxic compounds. The analysis encompassed the frequency of declaration by manufacturers, ingredients concentration in products, and emission concentrations. Out of the 133 substances, 107 were classified as carcinogenic, 32 as mutagenic, 20 as reprotoxic, 25 with chronic toxicity, 1 as a respiratory sensitizer, and 60 with endocrine disruptor potential. Several major chemical families are highlighted as significant contributors to health risks, among them:

Volatile organic compounds (VOCs)

Adverse health effects associated with VOCs are extensively documented in the literature. The European Commission and its Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) note that VOCs in e-liquids and emissions can cause respiratory tract irritation, leading to symptoms like coughing and breathing difficulties. Genotoxic and carcinogenic effects are mentioned, with acetaldehyde, formaldehyde, and benzene identified as established carcinogens and genotoxic compounds. Some VOCs also have the potential to cause reproductive toxicity. The National Academies of Science, Engineering, and Medicine express concerns about chronic health effects, including lung and cardiovascular diseases, associated with certain VOCs. Chronic toxicity is identified for various VOCs in line with their Classification, Labelling, and Packaging (CLP) classification.

Polycyclic aromatic hydrocarbons (PAH)

The thermal breakdown of substances and subsequent formation of PAH or vaporisation of PAH present in e-liquids during e-cigarette or HTP use can contribute to PAH exposure. In terms of health impact, several PAHs identified are classified as presumed human carcinogens according to their CLP classification, including benzo(a)anthracene, dibenzo(a,h)pyrene, chrysene, and dibenzo(a,h)anthracene. The Agency for Toxic Substances and Disease Registry (ATSDR) emphasizes that the most significant health endpoint for PAHs is cancer, although other effects such as pulmonary chronic toxicity and mutagenicity are also described. Specific PAHs like benzo(a)pyrene, dibenz(a,i)pyrene, and dibenz(a,l)pyrene have mutagenic potential based on their CLP classification.

Phenolic compounds

Phenolic compounds have also been identified in HTPs and e-cigarettes aerosols and e-liquids. Formation may originate from tobacco pyrolysis in HTP. For e-cigarettes, the formation and levels may be influenced by factors like PG:VG ratio, power, and puff duration. Among them, cresols (o-, m-, and p-) are classified as possible human carcinogens by the United States Environmental Protection Agency (US EPA), while catechol is considered a probable human carcinogen and a possible mutagen. Phenol is classified as a possible mutagen, and resorcinol is identified as an endocrine disruptor. Additionally, these substances exhibit other toxic effects, with cresols and resorcinol acting as respiratory irritants.

Metals and metalloids

Various metals and metalloids, such as arsenic, cobalt, lead, mercury, and selenium, have been found in aersols of HTP and aerosols and e-liquid of e-cigarettes. Exposure to some of these metals may pose a health hazard as several are classified as carcinogenic, notably by the International Agency for Research on Cancer (e.g., arsenic, beryllium, cadmium, chromium), while cobalt is considered probably carcinogenic. Nickel and lead are classified as possible carcinogens. Additionally, many of these metals are considered mutagenic or toxic to reproduction by the CLP classification. The metals also exhibit other toxic effects, such as the impact of lead on the central nervous system, arsenic's hemotoxic and hepatotoxic effects, and cadmium's role as a respiratory irritant.

Tobacco-related substances

Different tobacco-related substances have been identified in HTP, notably carbon disulfide which is classified as suspected toxic to reproduction and known for specific target organ toxicity after repeated exposure. It is associated with various adverse health issues, including coronary heart disease, retinal angiopathy, color perception problems, effects on peripheral nerves, psychophysiological effects, and central nervous system effects. Titanium dioxide (TiO2) has also been identidfied in HTP. This substance was classified as a suspected carcinogen in 2020 by the European Commission, however, the CMR classification of TiO2 has been invalidated by the European Court of Justice.

Device properties

During use of an e-cigarette, the e-liquid is heated to create an aerosol that is inhaled. This heating can lead to thermal decomposition of constituents and/or formation of new compounds, depending on the temperature, chemical composition, and duration of the heating (NAS, 2018). These decomposition products and new compounds may possess altered toxicity compared with their parent compounds. Other constituents identified in e-cigarette aerosols, include metals and silicate particles. These substances may add to the overall toxicity of the inhaled vapor (SCHEER, 2020). The main components that make up the e-cigarettes, such as battery, atomizer, coil, wick, and cartridge, may come in a range of different types and with settings that the user may or may not be able to alter. The various components may affect the amount and composition of the aerosol to be inhaled.

Properties related changes in watt, ohm, volt or temperature and impact on emissions.

Particles and e-liquid consumption

The review of studies on particle emissions as a function of watt, volt or temperature were divided into four groups dependent on method of analysis. These were e-liquid consumed, total deposition of particle mass on one filter, gravimetrically derived size distribution and real time measurement of particle size distributions and/or number of particles. As a function of increasing watt, volt or temperature, all studies in the two first groups showed an increase in e-liquid consumption (9 studies) and an increase in the mass of particulate matter (7 studies) respectively.

Seven studies identified used cascade impactors to investigate the particle size distribution. Particle size distribution may determine the location of deposition in the respiratory tract: in general, smaller particles penetrate more deeply into the lungs whereas larger particles are more likely to deposit in the upper respiratory tract. Four of the seven identified studies reported on effects of mass median aerodynamic diameter (MMAD) as a function of the volt, ohm, or watt. Two of these studies reported no significant effect whereas two studies reported an increase in MMAD as a function of watt. One explanation for the inconsistency in the results may be the different range of watts applied. Of the three other studies identified, one reported an increase in the total particulate mass with increasing volt applied. The mass was dominated by the fine particulate fraction for all voltages investigated. The latter finding was also reported in the study by Marocco et al., 2022. In addition, one study, investigated three different atomizers at either 200°C or 300°C. The authors reported an increase in the different particulate mass fractions investigated as a function of temperature for some combinations of PG:VG ratios and atomizers type. Device design, temperature and e-liquid composition may all affect the particle size distribution of the aerosol.

Nine studies were identified that investigated the real time particle size distributions and/or number of particles. The studies described either a bimodal or trimodal particle size distribution. In general, the results indicated an increase in particle number and size with increasing power applied.

Nicotine

All studies reported a wattage dependent increase in the amount of nicotine per puff. However, similar amounts of nicotine (µg) per mg mass vaped was observed. Thus, transfer of nicotine from the e-liquid to the aerosol appears to occur at the same rate as the solvents. However, the user may inhale a larger amount of aerosol and nicotine as the wattage is increased.

Volatile organic compounds (VOCs) identified in aerosolized e-liquid.

Several different VOCs have been identified in the e-cigarette aerosol. Three of the most frequent VOCs that were reported in the e-cigarette aerosols were formaldehyde, acetaldehyde and acrolein. These substances are known degradation products from the two common solvents glycerol and propylene glycol.

In the present report, the level of generated VOCs measured in the aerosols increased as a function of watt and temperature. In some of the included studies, an increase in wattage also induced an increase in the formation of VOCs per unit mass of generated aerosols. This shows that the increased formation of VOCs is not necessarily linear for all devices and settings. An explanation for this may be that the rate of evaporation exceeds the capacity of the wick to deliver e-liquid to the coil, resulting in increased coil temperatures. In addition, increased VOCs has been attributed to heat fluxes above the critical heat flux. In addition, other parameters such as air-hole opening and inter-drip interval (when direct dripping of e-liquid on the coil is used) as well as aging of the coil, may affect the VOC levels in the aerosol.

ROS formation identified in aerosolized e-liquid.

ROS have been detected in the emission from e-cigarettes. Formation of free radicals have been indicated to occur during (thermal) decomposition of the e-liquid solvents PG and VG (Bitzer et al., 2018a). In addition, the presence of flavoring chemicals have been reported to modulate, either by increasing or blocking the formation of free radicals dependent on the specific flavouring molecules, in the e-cigarettes aerosol (Bitzer et al., 2018b). In general, an increase in ROS with increasing watt or temperature was observed. However, ROS formation may in addition depend on the e-liquid composition and the air hole diameter of the e-cigarette. It is uncertain if the increase in ROS may be due to a concomitant increase in aerosolized e-liquid as this was not reported.

Metals identified in aerosolized e-liquid.

Metals can be detected in the aerosols from the e-cigarettes. Their sources may be impurities in the e-liquid itself as well as several metallic compartments in the device that are exposed to the e-liquid such as coil, wires connecting the battery to the coil, and the soldering between the different components. Both the watt used and aging of the coil during use may affect presence and amounts of metals present in the aerosol. Overall, the variation in metals measured in the aerosol between e-cigarettes may partly be explained by the different alloys used for the contruction of e-cigarettes, the e-liquid used and the power applied.

PAH identified in aerosolized e-liquid.

One study reported on PAH content in emissions from e-cigarettes as a function of changes in watt. No significant difference in sum of total PAH content was reported between the two wattages investigated, however, some PAHs were identified at the highest wattage only.

DIY practice

The Do-It-Yourself (DIY) practice is typically more favoured among experienced vapers who have been using e-cigarettes for an extended period compared to users who just started e-cigarette vaping. This DIY ethos is associated with a specific vaping subculture that distinguishes itself from the mainstream vaping culture focused on smoking cessation or harm reduction. While data on DIY prevalence is limited, there appears to be a trend toward an increase in such practices among e-cigarette users. The reasons for starting and maintaining DIY practices can be summarized in five main factors: cost savings, customisation, tailored nicotine levels, fun and novelty, and ingredients transparency.

Improper ingredient handling

Different risks can be associated with DIY practice notably because this involves handling concentrated nicotine, flavorings, and other ingredients, posing risks of leaking and spills during use. Accidental exposure to high concentrations of nicotine, especially through skin contact, is a concern during the creation of DIY e-liquids. Commercial e-liquids with dropper dispensers reduce the risk of accidental exposure, whereas concentrated nicotine samples, often used in DIY, may result in rapid exposure through open-neck bottles. Moreover, social media platforms, such as YouTube, may inadvertently encourage unsafe practices in DIY e-liquid mixing, as reported by Guy et al. (2019) including unconventional ways to test DIY liquid quality and the use of unqualified equipment.

Attractiveness

DIY e-liquids hold appeal for users due to the inherent customization aspect, allowing them to tailor the constituents to their preferences and enhance their vaporization experience. Long-term e-cigarette users, as seen in the study by Cox et al. (2019), found DIY mixing to be a crucial factor in sustaining their enjoyment of vaping. Situational factors, such as online communities, can contribute to the attractiveness of DIY practices, but concerns arise regarding age controls on social media platforms, potentially exposing youth to DIY ideas.The appeal of DIY products is closely tied to the attractiveness of characterizing flavors, as individuals can create their unique blends. Studies by Soule et al. (2016; 2020), and Schneller et al. (2018) suggest that flavor variety and the freedom to mix flavors may contribute to the use of e-cigarettes among both adolescents and adults. However, there is a lack of research on DIY practice influence attractiveness and addiction. More studies are needed to understand the potential effects on e-cigarette users who create their own e-liquids.

Ingredient quality and safety

The quality and safety of ingredients in DIY e-liquids vary, with motivations for DIY ranging from perceived control over ingredients to differing views on the quality compared to commercial products. DIY e-liquids may include flavorings not specifically intended for e-cigarette use, raising concerns about unknown aerosolization and inhalation risks. Users may add various additives, such as sweeteners and cooling agents, known to increase e-cigarette appeal and suppress nicotine's bitterness making nicotine-products more attractive. Some individuals experiment with adding illicit drugs or psychoactive substances to DIY e-liquids. Studies analyzing DIY e-liquids reveal discrepancies in nicotine concentrations potential leading to exposure to higher nicotine concentrations from inhalation or other routes of exposure than anticipated. The safety profiles of DIY e-liquids are generally similar to commercial ones, but the use of unusual additives or ingredient combinations raises questions about additional toxicity.

Reactivity/Ageing

The shelf-life of e-liquids may be limited as their components can degrade and interact, potentially leading to the formation of new substances. When e-liquids come into contact with the metal components of e-cigarette devices, there is a possibility of metal transfer from the device to the liquid. In addition, continuous use may contribute to the deterioration of important parts like the cartomizer, increasing the risk of substance leakage into the e-liquid.

Metals

E-liquids interact with different metallic components in e-cigarettes, and research indicates that storing them in the clearomizer for a few days may lead to an elevation in the levels of certain metals, such as lead and zinc, within the e-liquid. Jitareanu et al. (2022) demonstrated that the composition of the e-liquid can also impact the extent to which metals dissolve from the compartments of e-cigarettes.

Nicotine and nicotyrine

The concentration of nicotyrine, a break-down product of nicotine (and nicotyrine-nicotine-ratio; NNR) in the e-liquid was reported to increase during storage (Martinez et al., 2015). Furthermore, the amount of nicotine was reported to decrease over a period of 6 months except for two products with mint flavour, indicating that degradation of nicotine may occur (Kosarac et al., 2023).

Formation of e-liquid solvent adducts

Two studies explored the formation of adducts between various additives, such as flavoring molecules, and e-liquid solvents. Erythropel et al. (2019) found that propylene glycol adducts were formed due to flavoring aldehydes in laboratory-made e-liquids, with acetal formation increasing at room temperature, particularly with higher propylene glycol concentrations. Another study by Gschwend et al. (2023) investigated adducts between a broader range of flavoring molecules and solvents (methanol, PG, or VG), revealing that, out of 36 flavoring molecules, 14 reacted with methanol, and 12 reacted with PG or VG over four weeks of storage. Both studies demonstrated the formation of acetals in commercial e-liquids, indicating that flavoring molecules react with e-liquid solvents during storage.

pH

A single study examined the impact of storage on the pH of e-liquids. The findings from Fairchild (2021) indicated that the pH of the investigated e-liquid remained unaffected by the storage conditions.

Discussion and conclusion

In summary, the research reveals the presence of harmful substances as ingredients and in the emissions of e-cigarettes and heated tobacco products. Factors like user behavior and device settings of e-cigarettes may influence substance generation as well as substance exposure. Important potential health concerns include the formation of new compounds during product use, the potential transfer of harmful substances from e-liquids to aerosols, and increased metal content in e-liquids due to device components. DIY practices add variability to aerosol content, posing potential health risks. Actions are needed to characterize and regulate substances in the emissions, including those from nicotine-free products, and inform users about associated risks.

Acronyms

APS	:	Aerodynamic particle sizer
CBD	:	Cannabidiol
CPC	:	Condensation particle counter
DIY	:	Do It Yourself
ECF	:	E-Cigarette Forum
ECIG	:	E-cigarettes
E-cigarette	:	Electronic cigarette
EU	:	European Union
EVALI	:	E-cigarette or Vaping Use-Associated Lung Injury
G	:	Glycerine
GC-MS	:	Gas chromatography mass spectrometry
HPLC	:	High performance liquid chromatography
JATC	:	Joint Action on Tobacco Control
LOD	:	Limit Of Detection
LOQ	:	Limit Of Quantification
MeSH	:	Medical Subject Headings
MMAD	:	Mass Median Aerodynamic Diameter
MOUDI	:	Micro-orifice uniform deposit impactor
PAH	:	Polycyclic aromatic hydrocarbons
PAMS	:	Portable aerosol mobility spectrometer
PG	:	Propylene Glycol
PPM	:	Parts Per Million
ROS	:	Reactive oxygene species
SMPS	:	Scanning mobility particle sizer
THC	:	Tetrahydrocannabinol
TPD	:	Tobacco Products Directive
TPM	:	Total particulate matter
TSNA	:	Tobacco-Specific Nitrosamine
VG	:	Vegetable Glycerine
VOCs	:	Volatile Organic Compounds

I. Introduction

Within the scope of the 2nd Joint Action on Tobacco Control (JATC 2) involving the collaborative efforts from various European Union (EU) member States and to accurately evaluate the health impact of novel tobacco products and electronic cigarettes, it is essential to assess products ingredients, additives, devices and emissions in relation to their function and toxicological information. This objective falls under the purview of Work Package 7. Within this work package, one of the aims is to categorize novel tobacco products into distinct categories based on their health risk potential.

Previous works conducted within this European project (2023) enabled all the substances declared by the manufacturers of electronic cigarettes and heated tobacco products along with the emissions of both products to be prioritised into three categories based on hazard criteria:

1. High-priority substances
2. Substances requiring additional data
3. Lack of data needed for categorization

The objective of this report is to describe the health risk profiles associated with the list of high-priority emitted and declared substances identified for electronic cigarettes and heated tobacco products. In addition, the results of another JATC2 report (2022) outlined several properties such as the mixture of substances, device properties, Do It Yourself (DIY) practice, and the ageing process that are important for the health risk assessment of e-cigarettes. Through a literature review, an evaluation of these properties' respective impacts on the composition of the e-liquid and the resulting emissions was performed. The synthesis of results has led to the elaboration of the present report (D7.3) focusing on the relevant health risks of electronic cigarettes and heated tobacco products.

Aim of the report

The aim of the report is to identify healh risks associated with the use of e-cigarettes and heated tobacco products including an analysis of data on emissions found in literature and data on declared ingredients by manufacturers in both products. Particular attention has been given to the impact of different properties when using electronic cigarettes, including :

1) Device properties

With the objective to systematically review and summarize available evidence on how electronic cigarette device properties affect the composition of emissions from electronic cigarettes.

More specifically, we investigated the effects of:

- Properties related to changes in watt, ohm or volt or temperature
- Different coil materials/alloys (filaments)
- Different properties of the wick
- Other properties

on the emission of nicotine, volatile and/or semi-volatile organic compounds, metals, polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), reactive oxygen species (ROS), free radicals, particle size distribution and/composition, or other constituents in the aerosol.

2) DIY practice

The objective was to review and summarize the evidence about the DIY practice associated with e-cigarette use. More specifically we focused on:

- The records of practice,
- The motivations and behaviours of e-cigarette users using self-made e-liquids and
- The risk associated with DIY practice.

3) Reactivity/Ageing

The objective of this section is to investigate the effect of storage with an analysis of the impact of e-liquid reactivity and ageing. Several aspects were examined:

- Metals
- Nicotine and nicotyrine
- Formation of e-liquid solvent adducts
- pH

II. Methods

Health hazards

Analysed substances

The list of high-priority substances, found in both e-cigarettes and heated tobacco products, identified as Category 1 and associated with a higher hazard potential has been estasblished in a previous report (JATC2 2023). This list of 133 unique substances, after eliminating duplicates (17 substances), includes data on products ingredients declared by manufacturers (39 substances) and emissions data from a literature review (111 substances). For this work, the following information on substances was collected according to the methodology described in the previous report (JATC2 2023):

- Concentrations of ingredients in ppm within the product;
- Frequency of the presence of these ingredients in e-liquids/heated tobacco products.
- Emissions concentration when available;

Identification of health effects

After grouping the substances into chemical classes using Medical Subject Headings (Mesh[1]), the health effects associated with the main families were precised. To produce a summary of the health effects, the data from the available bibliography, essentially from grey literature, were consolidated.

Impacting properties

Device properties

Protocol

This part of the report, based on a systematic review process on effects of electronic cigarette device properties on composition of emission, was conducted in accordance with a protocol (NIPH, 2024) based on the NIPH methods book (NIPH, 2021) and the Cochrane Handbook of Systematic Reviews of Interventions (Higgins et al., 2019).

Search strategy

All literature searches were conducted by a research librarian at NIPH. The search was originally performed in December 2020 (MEDLINE (Ovid), Embase (Ovid) and Web of science) and in February 2021 (Cochrane Database of Systematic Reviews) for the task of making an interactive research map on e-cigarettes (Becher et al., 2021). The search was updated in November 2021 (Becher et al., 2022), where reviews were included in an umbrella review on adverse effects of e-cigarettes use. The search was further updated in March 2023, for the present report. From almost 10,000 articles identified in the search for the interactive research map, 530 were categorized under the umbrella code: model and/or physical and/or chemical analyses (Becher et al., 2021). Overall, for the present report, the updated search in 2021 and 2023 gave 5,521 articles, and combined with the previous identified 530, a total of 6,047 articles were screened on abstract for the present work after removal of duplicates. The search string is presented in Appendix II.

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[1] https://www.ncbi.nlm.nih.gov/mesh

Study eligibility criteria

We included studies that investigated the effects of properties related to changes in watt, ohm or volt, temperature of the heating device, different coil materials/alloys (filaments) as well as different properties of the wick on the emission of nicotine, volatile and/or semi-volatile organic compounds, metals, polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), reactive oxygen species (ROS), free radicals, particle size distribution and/composition or other constituents in the aerosol. To compare the impact of changes in e-cigarette settings on emissions, identical e-liquid and puffing topography had to be used across the comparisons in the same study. Research funded by or otherwise linked to tobacco/electronic cigarette industry was not included. Because of the amount of litereature identified and the time frame of the project, we deviated from our protcol in that we excluded human studies that measured emissions from e-cigarettes users (exhaled breath and/or secondary exposure). The inclusion criteria for the selection of articles are shown in Table 1.

Study selection

The identified titles and abstracts were screened against the inclusion criteria by two researchers independent of each other, discrepancies were resolved by discussion. Relevant papers were assessed in full text by two researchers independently and discrepancies resolved by discussion.

Study quality

The Risk Of Bias (ROB) evaluation was based on the Oral Health Assessment Tool (OHAT) protocol for in vitro studies (Rooney, 2015), and in addition two criteria were retrieved from the systematic review by Prueitt and co-workers (2020). The risks of bias questions were:

- Can we be confident in the exposure characterization?
- Were experimental conditions identical across study groups?
- Can we be confident in the outcome assessment?
- Did the study have an adequate number of replicates per study group?
- Did the study employ appropriate statistical approaches?
- Were the properties (property) investigated, such as - watt, ohm or volts of the e-cigarette or different brands, components, adequately randomized/ weighted randomization?
- Was allocation to study groups adequately concealed?
- Were the research personnel blinded to the study group during the study?
- Were outcome data complete without attrition or exclusion from analysis?
- Were all measured outcomes reported?

The specific questions and overall evaluation of ROB was based on The Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (NTP 2019) and was performed by two researchers. The studies rated as probably high or definitely high risk of bias were excluded for further evaluation. The full description of RoB assessment is shown in Appendix I.

We assessed the risk of bias of the included studies and assessed our confidence in the results about the e-liquid consumption and e-cigarette power settings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. We deviated from the protocol as we only graded the studies that investigated e-liquid consumption as a function of wattage. Graded outcome is presented in our GRADE table (Appendix VI - GRADE assessment of the studies that investigated e-liquid consumption as a function of wattage – GRADE assessment of the studies that investigated e-liquid consumption as a function of wattage).

Data extraction

One author from the working group collected data from the studies and another author checked that the relevant information was correctly extracted. Disagreements were solved by consensus.

We collected information on the full reference, when and where the study was conducted, information on the device and liquids used, number and type of devices included and puffing protocol/topography, emission outcomes measured, measuring methods (aerosol collection technique and type of chemical analysis) and the reported results.

Table 1: Inclusion criteria for the selection of articles.

Population	Electronic cigarettes
Exposure 1	Properties related to changes in watt, ohm, volt, or temperature setting of the heating device.
Comparison 1	A different measure of watt, ohm, volt, or temperature of the heating device keeping every other parameter constant.
Exposure 2	Coil material alloy (filament)
Comparison 2	Another coil material/alloy (filament) keeping every other parameter constant.
Exposure 3	Properties of the wick
Comparison 3	Another property of the wick keeping every other parameter constant.
Exposure 4*	One e-cigarette type/brand or component
Comparison 4*	Another e-cigarette type/brand or component from another manufacturer with same e-liquid and same puffing topography keeping every other parameter constant.
Outcome	Composition of the emission, specifically: Nicotine Volatile and/or semi volatile organic compounds including glycerol and propylene glycol. Metals PAHs and TSNAs ROS, free radicals Particle size distribution and/ composition Other constituents in the aerosol or gas phase*
Study design	Studies with a control group using the same e-liquid(s) and same puffing topography.
Publication time	No restrictions. If very heterogeneous, sensitivity analysis per year will be performed.
Country/ context	No restrictions
Language	No restrictions in the searches, but we only assessed in full text and included studies in Danish, English, Norwegian and Swedish

*We deviated from the protocol in that this comparison was not performed.

DIY practice

For the literature search to answer the research questions concerning DIY e-liquids (What is done? What it can lead to? Records of practice), the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed when applicable. The search was conducted in databases using specific keywords, duplicate papers were eliminated and finally abstracts and titles were screened for relevance. An additional non-exhaustive search for relevant publications was conducted on Google Scholar.

The search was conducted in June 2023 and was carried out in three bibliographic databases, Web of Knowledge, Embase and PubMed, using the following search equation and keywords mentioned in Appendix II : Search strings: Search strings. The search date range was unrestricted.

To be considered for screening, full text must be publicly available and must be in English. Article titles and abstracts were then screened for relevance to the research questions.

Reactivity/Ageing

A search was performed in the following databases: Pubmed, Embase and Scopus. The search string is provided in Appendix II : Search strings: Search strings. Studies were included if they reported on the effects of ageing, storage on e-liquid composition. As the search returned few included studies, an additional search was performed in EPPI-Reviewer 6, searching for keywords (Appendix II : Search strings: Search strings) in title and abstract, in the articles screened for the search performed for device properties in this report. Studies on tetrahydrocannabinol/cannabidiol (THC/CBD) were excluded.

III. Results and Discussion

I. Health hazards

Hazard classification

To assess the health effects associated with electronic cigarettes and heated tobacco products, the ingredients declared by manufacturers and substances detected in emissions were analysed according to their presence in different hazard classifications. Details of the classification of the 133 substances considered to represent the greatest hazards are given in Appendix III. These substances are classified in one of the following categories as:

- Known human carcinogen (Category 1A), presumed (Category 1B), or suspected (Category 2) within the CLP harmonised classification, or by equivalence with one of the other classifications examined;
- Mutagenic or toxic for reproduction (Category 1A), presumed (Category 1B), or suspected (Category 2) within the CLP harmonised classification;
- Endocrine disruptors under the BKH or DHI (Category 1 or 2), or SIN List classifications, with a positive conclusion from the US EPA, or classified in Category 3a (insufficient data) or 3b (no data) by BKH or DHI but presenting at least one relevant study at the time of its classification in the TEDX list;
- As having specific toxicity for specific target organs after repeated exposure (STOT RE 1 or STOT RE 2) within the CLP harmonised classification;
- Respiratory sensitisers (Category 1 and sub-category 1A or 1B) within the CLP harmonised classification;
- Or very highly acutely toxic (Acute Tox. Category 1) within the CLP harmonised classification.

It is important to note that certain compounds are regulated and prohibited by the Tobacco Product Directive (TPD) n°2014/40/EU for e-cigarettes and HTP: these include substances that are carcinogenic, mutagenic, or toxic to reproduction (CMR), vitamins, and stimulants such as caffeine or taurine. Indeed, regulations, notably on CMR compounds, apply to additives, and not to ingredients, that explain the presence of such substances, even for data declared by manufacturers. An additive is added on purpose while an ingredient is a substance present in the final product. An additive can be declared as an ingredient, but some chemicals that appear after chemical reactions between additives might also be declared as ingredients. Manufacturers might have declared only additives (i.e. what they added to the product) whereas some other manufacturers declared ingredients (i.e. what they have found after an analysis of the product, not the initial composition).

Characteristics of substances in products

Once the hazard classifications had been identified, the frequency of declaration of ingredients as well as their concentration in the product, and the concentration of specific substances in emissions were determined. This was carried out for the emission substances identified in the literature review (Erreur ! Source du renvoi introuvable.) and for declared ingredients by manufacturers (Erreur ! Source du renvoi introuvable.) for electronic cigarettes and heated tobacco. Moreover, the chemical family of these substances has been identified in these tables. Based on the results from Erreur ! Source du renvoi introuvable. and Erreur ! Source du renvoi introuvable., of the 133 substances listed, only 17 ingredients can also be found in the emissions regardless of the examined product (Table 4). Regarding data on emissions from literature, out of the 111 high-priority emission substances, 59 substances are common to e-cigarettes and HTP, 12 and 40 substances are specific to HTP and e-cigarettes respectively. For data on ingredients declared by manufacturers, out of the 39 high-priority ingredients only 1 substance is common between both products, 3 are specific to HTP, and 35 to e-cigarette.

Table 2: Summary of the frequency and concentrations of Category 1 substances found in emissions and identified by a literature review for e-cigarettes and heated tobacco products.

	CAS number	Substance	Family	E-cigarettes	HTP
				Emission concentrations (µg/m3)	Emission concentrations (µg/item)
Literature	57653-85-7	1,2,3,6,7,8-hexa CDD	Dioxin	3,24E-04	x
	40321-76-4	1,2,3,7,8-penta CDD	Dioxin	3,03E-04	x
	57117-41-6	1,2,3,7,8-penta CDF	Furan	2,91E-04	x
	107-06-2	1,2-dichloroethane	Chlorinated	8,00E-02	x
	78-87-5	1,2-dichloropropane	Chlorinated	2,00E-02	x
	106-99-0	1,3-butadiene	Alkene	4,07E+01	3,28E-01
	106-46-7	1,4-dichlorobenzene	Chlorinated	2,00E-02	x
	26148-68-5	1-amino-3-methyl-9H-pyrido-[2,3,b] indole (MeAaC)	Heterocyclic aromatic	8,86E-02	8,00E+02
	930-55-2	1-Nitrosopyrrolidine (NPYR)	Nitroamine	2,27E+00	x
	57117-31-4	2,3,4,7,8-penta CDF	Furan	2,93E-04	x
	1746-01-6	2,3,7,8-tetra CDD	Dioxin	3,04E-04	x
	51207-31-9	2,3,7,8-tetra CDF	Furan	2,87E-04	x
	87-62-7	2,6-dimethylaniline	Amine	9,05E-03	1,52E+02
	105650-23-5	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)	Heterocyclic aromatic	1,04E-01	x
	67730-11-4	2-amino-6-methyldipyrido[1,2-a:3’,2’-d]imidazole (Glu-P-1)	Heterocyclic aromatic	6,82E-02	x
	67730-10-3	2-aminodipyrido[1,2-a:3’,2’-d]imidazole (Glu-P-2)	Heterocyclic aromatic	8,60E-02	x
	91-59-8	2-aminonaphthalene	Amine	6,23E-02	2,40E+01
	79-46-9	2-nitropropane	Nitrogen compounds	2,08E+00	6,18E+03
	62450-06-0	3-amino-1,4-dimethyl-5H-pyrido(4,3-b)indole (Trp-P-1)	Heterocyclic aromatic	7,00E-02	x
	62450-07-1	3-Amino-1-methyl-5H-pyrido[4,3-b] indole (Trp-P-2)	Heterocyclic aromatic	8,05E-02	x
	96-24-2	3-chloro-1,2-propandiol	Chlorinated	4,30E+04	9,94E+00
	92-67-1	4-aminobiphenyl	Amine	1,34E-02	1,60E+01
	108-10-1	4-methyl-2-pentanone	Ketone	1,20E-01	2,70E-01
	3697-24-3	5-methylchrysene	PAH	1,20E-01	x
	75-07-0	Acetaldehyde*	Aldehyde	9,45E+04	2,70E+02
	60-35-5	Acetamide	Amide	3,43E+01	2.93
	107-02-8	Acrolein*	Aldehyde	1,22E+05	1,70E+01
	79-06-1	Acrylamide	Amide	8,71E+01	1,44E+00
	107-13-1	Acrylonitrile	Nitrogen compounds	4,57E+01	1,80E-01
	71-43-2	Benzene	Monocyclic aromatic	8,76E+00	7,70E-01
	92-87-5	Benzidine	Amine	4,14E-03	x
	56-55-3	Benzo(a)anthracene	PAH	2,61E-02	2,02E+03
	50-32-8	Benzo(a)pyrene	PAH	3,80E-02	8,12E+02
	205-99-2	Benzo(b)fluoranthene	PAH	1,21E-01	6,47E+02
	271-89-6	Benzo(b)furan	PAH	6,86E+00	2,60E-02
	195-19-7	Benzo(c)phenanthrene	PAH	3,84E-02	8,07E+02

	192-97-2	Benzo(e)pyrene	PAH	4,90E-05	x
	202-33-5	Benzo(j)aceanthrylene	PAH	7,41E-02	x
	207-08-9	Benzo(k)fluoranthene	PAH	8,47E-02	3,96E+02
	75-27-4	Bromodichloromethane	Bromo-chlorinated	2,00E-02	x
	331-39-5	Caffeic acid	Acid	3,41E+02	x
	630-08-0	Carbon monoxide	Carbon oxide	8,91E+03	4,00E-02
	120-80-9	Catechol	Phenol	3,67E+01	1,15E+01
	67-66-3	Chloroform	Chlorinated	2,00E-01	x
	218-01-9	Chrysene	PAH	1,51E-01	1,98E+03
	123-73-9	Crotonaldehyde	Aldehyde	1,09E+02	8,25E+00
	27208-37-3	Cyclopenta(c,d)pyrene	PAH	x	5,98E+02
	53-70-3	Dibenz(a,h)anthracene	PAH	8,85E-02	1,00E+02
	189-64-0	Dibenz(a,h)pyrene	PAH	1,01E-01	x
	189-55-9	Dibenz(a,i)pyrene	PAH	9,40E-02	x
	191-30-0	Dibenz(a,l)pyrene	PAH	1,81E-01	x
	64-17-5	Ethanol*	Alcohol	1,43E+04	x
	100-41-4	Ethylbenzene	Monocyclic aromatic	4,15E-01	2,46E-01
	75-21-8	Ethylene oxide	Epoxide	5,13E+01	1,80E-01
	50-00-0	Formaldehyde*	Aldeyde	3,77E+07	1,16E+01
	110-00-9	Furan	Furan	4,00E+01	1,48E+01
	556-52-5	Glycidol	Epoxide	2,66E+02	2,86E+00
	107-22-2	Glyoxal	Aldehyde	9,78E+02	3,11E+00
	302-01-2	Hydrazine	Hydrazine	2,91E+00	x
	123-31-9	Hydroquinone	Ketone	8,89E+01	6,34E+00
	193-39-5	Indeno(1,2,3-cd)pyrene	PAH	3,60E-02	x
	78-79-5	Isoprene	Alkene	3,14E+01	2,10E+00
	108-39-4	m-cresol	Phenol	8,07E+00	3,00E-02
	1634-04-4	Methyl tert-butyl ether	Ether	4,00E-01	x
	75-09-2	Methylene chloride	Chlorinated	7,90E-01	1,50E+00
	91-20-3	Naphthalene	PAH	5,78E-01	2,81E+03
	110-54-3	n-hexane	Alkane	1,30E+00	9,00E-01
	98-95-3	Nitrobenzene	Monocyclic aromatic	1,63E+01	4,60E+01
	75-52-5	Nitromethane	Nitrogen compounds	1,21E+01	3,84E+04
	924-16-3	N-Nitrosodibutylamine (NDBA)	Nitroamine	2,96E+00	x
	1116-54-7	N-Nitrosodiethanolamine (NDELA)	Nitroamine	3,21E+00	x
	55-18-5	N-Nitrosodiethylamine (NDEA)	Nitroamine	4,40E-01	x
	62-75-9	N-Nitrosodimethylamine (NDMA)	Nitroamine	6,77E-01	x
	59-89-2	N-nitrosomorpholine (NMOR)	Nitroamine	3,93E-01	x
	100-75-4	N-nitrosopiperidine (NPIP)	Nitroamine	1,22E-01	x
	90-04-0	o-anisidine	Amine	3,30E-02	1,66E+02
	95-48-7	o-cresol*	Phenol	1,10E+01	5,00E-02
	95-53-4	o-toluidine	Amine	1,61E-01	9,57E+02
	106-44-5	p-Cresol	Phenol	1,47E+01	6,00E-02
	108-95-2	Phenol*	Phenol	2,36E+01	1,13E+00

	75-56-9	Propylene Oxide	Epoxide	2,23E+01	6,91E+04
	110-86-1	Pyridine*	Heterocyclic aromatic	1,67E+02	6,20E+00
	91-22-5	Quinoline	Heterocyclic aromatic	4,57E+00	3,00E-03
	108-46-3	Resorcinol	Phenol	2,35E+01	3,00E-02
	100-42-5	Styrene	Monocyclic aromatic	1,60E-01	6,10E-01
	127-18-4	Tetrachloroethylene	Chlorinated	2,60E-01	x
	108-88-3	Toluene	Monocyclic aromatic	7,01E+00	1,71E+00
	79-01-6	Trichloroethylene	Chlorinated	2,00E-02	x
	108-05-4	Vinyl Acetate	Ester	1,56E+01	x
	75-01-4	Vinyl Chloride	Chlorinated	9,29E-01	3,54E+03
	98-01-1	Furfural*	Furan	x	3,14E+01
	98-00-0	2-furanmethanol*	Furan	x	2,60E+01
	591-78-6	2-Hexanone*	Ketone	x	1,00E-01
	67-64-1	Acetone*	Ketone	x	2,60E+01
	75-86-5	Acetone cyanohydrin	Ketone	x	6,50E-01
	120-12-7	Anthracene	PAH	x	3,00E+02
	75-15-0	Carbon disulfide	Sulfide	x	3,00E-01
	75-00-3	Chloroethane	Chlorinated	x	1,30E-01
	74-87-3	Chloromethane	Chlorinated	x	1,11E+01
	96-33-3	Methylacrylate*	Acid	x	4,40E-01
	85-01-8	Phenanthrene	PAH	x	2,00E+03
	123-35-3	β-myrcene*	Alkene	x	4,00E-01
	7440-38-2	Arsenic	Inorganic	1,40E+00	x
	7440-48-4	Cobalt*	Inorganic	6,38E-01	x
	7439-92-1	Lead*	Inorganic	7,89E-02	2,23E+00
	7439-97-6	Mercury	Inorganic	2,98E-02	9,90E+02
	7782-49-2	Selenium	Inorganic	1,13E+00	1,27E+00
	7440-41-7	Beryllium	Inorganic	1,34E+00	x
	7440-43-9	Cadmium	Inorganic	7,81E-01	x
	7440-47-3	Chromium*	Inorganic	2,87E+00	x
	7440-02-0	Nickel*	Inorganic	1,50E-01	x

*: Susbtances declared as ingredients by manufacturers and found in emissions according to literature
x: No data available
☒: Specific substance of HTP
☒: Specific substance of e-cigarette

Table 3: Summary of the frequency and concentrations of Category 1 substances declared as ingredients by manufacters for e-cigarette and heated tobacco product.

	CAS Number	Substance	Family	E-cigarettes		HTP	
				Frequency	**Mean proportion in the product (ppm)**	**Frequency**	**Mean proportion in the product (ppm)**
Declared	64-17-5	Ethanol*	Alcohol	14370	148060	2	52490
	65-85-0	Benzoic acid	Acid	2476	13875	x	x
	77-93-0	Triethyl citrate	Acid	913	6185	x	x
	69-72-7	Salicylic acid	Acid	593	10217	x	x
	77-53-2	Cedrol	Terpene	440	5533	x	x
	77-83-8	Ethyl methylphenylglycidate	Acid	248	6936	x	x
	123-35-3	Myrcene*	Alkene	162	3319	x	x
	119-36-8	Methyl salicylate	Acid	128	5680	x	x
	98-00-0	Fufurfyl alcohol*	Furan	102	8833	x	x
	89-82-7	Pulegone	Ketone	78	1604	x	x
	98-01-1	Fufural*	Aldehyde	59	3029	x	x
	75-07-0	Acetaldehyde*	Aldehyde	44	149390	x	x
	7440-02-0	Nickel*	Inorganic	42	248952	x	x
	7439-92-1	Lead*	Inorganic	26	12279	x	x
	78-59-1	Isophorone	Ketone	20	1547	x	x
	98-02-2	Furfuryl mercaptan	Furan	18	2361	x	x
	7440-47-3	Chromium*	Inorganic	17	12257	x	x
	76-49-3	Bornyl acetate	Terpene	16	2591	x	x
	67-64-1	Acetone*	Ketone	9	22621	x	x
	110-86-1	Pyridine*	Heterocyclic aromatic	9	11967	x	x
	7440-48-4	Cobalt*	Inorganic	9	1205	x	x
	128-37-0	Butylated hydroxytoluene	Phenol	8	1317	x	x
	108-95-2	Phenol*	Phenol	6	2500	x	x
	548-62-9	Methylrosanilinium chloride	Amine	5	8820	x	x
	541-02-6	Decamethylcyclopentasiloxane	Siloxane	5	1358	x	x
	97-99-4	Tetrahydrofurfuryl alcohol	Furan	4	20000	x	x
	97-88-1	N-butyl methacrylate	Acid	4	2750	x	x
	591-78-6	2-Hexanone*	Ketone	3	18687	x	x
	95-48-7	o-cresol*	Phenol	3	4000	x	x
	1303-86-2	Boron oxide	Inorganic	3	2168	x	x
	1333-86-4	Carbon black	Other	2	12987	x	x
	50-00-0	Formaldehyde*	Aldehyde	1	48580	x	x
	4170-30-3	Crotonaldehyde	Aldehyde	1	11907	x	x
	110-15-6	Succinic acid	Acid	1	11500	x	x
	107-02-8	Acrolein*	Aldehyde	1	8930	x	x
	96-33-3	Methyl acrylate*	Acid	1	4187	x	x
	71-55-6	Methylchloroform	Chlorinated	x	x	44	40000
	13463-67-7	Titanium dioxide	Inorganic	x	x	113	2089

	77-90-7	Acetyltributyl citrate	Acid	x	x	78	376

*: Susbtances declared as ingredients by manufacturers and found in emissions according to literature
x: No data available
☒: Specific substance of HTP
☒: Specific substance of e-cigarette

Table 4: Common substances found in ingredient data from manufacturers and emission data from literature.

CAS number	**Substance**	**Family**	**E-cigarettes**			**HTP**		
			Frequency	**Mean proportion in the product (ppm)**	**Emission concentrations (µg/m3)**	**Frequency**	**Mean proportion in the product (ppm)**	**Emission concentrations (µg/item)**
75-07-0	Acetaldehyde	Aldehyde	44	149390	9,45E+04	x	x	2,70E+02
107-02-8	Acrolein	Aldehyde	1	8930	1,22E+05	x	x	1,70E+01
64-17-5	Ethanol	Alcohol	14370	148060	1,43E+04	2	5,25E+04	x
50-00-0	Formaldehyde	Aldeyde	1	48580	3,77E+07	x	x	1,16E+01
95-48-7	o-cresol	Phenol	3	4000	1,10E+01	x	x	5,00E-02
108-95-2	Phenol	Phenol	6	2500	2,36E+01	x	x	1,13E+00
110-86-1	Pyridine	Heterocyclic aromatic	9	11967	1,67E+02	x	x	6,20E+00
98-01-1	Furfural	Furan	59	3029	x	x	x	3,14E+01
98-00-0	2-furanmethanol	Furan	102	8833	x	x	x	2,60E+01
591-78-6	2-Hexanone	Ketone	3	18687	x	x	x	1,00E-01
67-64-1	Acetone	Ketone	9	22621	x	x	x	2,60E+01
96-33-3	Methylacrylate	Acid	1	4187	x	x	x	4,40E-01
123-35-3	β-myrcene	Alkene	162	3319	x	x	x	4,00E-01
7440-48-4	Cobalt	Inorganic	9	1205	6,38E-01	x	x	x
7439-92-1	Lead	Inorganic	26	12279	7,89E-02	x	x	2,23E+00
7440-47-3	Chromium	Inorganic	17	12257	2,87E+00	x	x	x
7440-02-0	Nickel	Inorganic	42	248952	1,50E-01	x	x	x

x: No data available
☒: Specific substance of e-cigarette

Health impact

Of all the substances identified as representing the highest hazard potential, volatile organic compounds (VOCs), tobacco-specific nitroamines (TSNAs), polycyclic aromatic hydrocarbon (PAH), and metals are particularly significant contributors. Indeed, among the high-priority substances were found:

- 107 classified as carcinogenic;
- 32 classified as mutagenic;
- 20 classified as reprotoxic;
- 25 with chronic toxicity (STOT RE);
- 1 as respiratory sensitisers;
- 60 with an endocrine disruptor potential.

Volatile organic compounds (VOCs)

HTP and e-cigarettes emit toxic compounds. About thirty VOCs have been reported, which include carbonyls, (i.e acetaldehyde, formaldehyde, acrolein, etc.), halogenated compounds (i.e. bromodichloromethane, chloroform, tetrachloroethylene, etc.), and aromatic hydrocarbons (i.e. benzene, toluene, styrene, etc.). These substances may be generated from thermal decomposition and their levels may increase gradually with increasing temperature. Upon heating a mixture of glycerol and propylene glycol in e-cigarettes, various aldehydes are produced. Since glycerol and propylene glycol are also found in HTP, it is likely that aldehydes are generated with use of these products as well (WHO 2021)No. 1029.

Adverse health effects associated with VOC are widely described in the literature. Indeed, the European Commission and its Scientific Committee on Health, Environmental, and Emerging Risks (SCHEER) conclude in their final Opinion on electronic cigarettes that these substances can induce respiratory tract irritation: VOCs present in e-liquids and the resulting emissions can irritate the respiratory system, resulting in symptoms like coughing, sore throat, and breathing difficulties. Genotoxic and carcinogenic effects are also mentioned, acetaldehyde, formaldehyde, and benzene are established carcinogens and genotoxic compounds according to their Classification, labelling, and packaging of chemicals (CLP) classification. Several VOCs such as chloroform, styrene, and toluene have a reprotoxic potential, according to the CLP Regulation 1272/2008. The National Academies of Science, Engineering, and Medicine (NASEM) have also raised concerns about chronic health effects including lung diseases as well as cardiovascular heart diseases associated with formaldehyde, acrolein, and acetaldehyde (NASEM 2018)Engineering, and Medicine for free.","ISBN":"978-0-309-46834-3","language":"en","note":"DOI: 10.17226/24952","source":"www.nap.edu","title":"Public Health Consequences of E-Cigarettes","URL":"https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes","author":[{"literal":"NASEM"}],"accessed":{"date-parts":[["2020",11,27]]},"issued":{"date-parts":[["2018",1,23]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . Chronic toxicity has also been identified for other VOCs (i.e. benzene, chloroform, styrene, toluene, etc.) in line with their CLP classification.

Tobacco-specific nitroamines (TSNAs)

Although nicotine is not present in this list, several tobacco-specific nitrosamines (TSNA) derived from nicotine and other tobacco alkaloids were identified. Among them: N-Nitrosodibutylamine (NDBA), N-Nitrosodiethanolamine (NDELA), N-Nitrosodiethylamine (NDEA), N-Nitrosodimethylamine (NDMA), N-nitrosomorpholine (NMOR) as well as N-nitrosopiperidine (NPIP). TSNAs originate from tobacco leaves and are produced through the nitrosation of amines during the curing process (NASEM 2018)Engineering, and Medicine for free.","ISBN":"978-0-309-46834-3","language":"en","note":"DOI: 10.17226/24952","source":"www.nap.edu","title":"Public Health Consequences of E-Cigarettes","URL":"https://www.nap.edu/catalog/24952/public-health-consequences-of-e-cigarettes","author":[{"literal":"NASEM"}],"accessed":{"date-parts":[["2020",11,27]]},"issued":{"date-parts":[["2018",1,23]]}}}],"schema":"https://github.com/citation-style-language/

schema/raw/master/csl-citation.json”} . All TSNA mentioned previously are classified as either probable (group 2A) or possible (group 2B) carcinogens by the International Agency for Research on Cancer (IARC). The SCHEER report indicates that exposure to this type of substance can lead to the development of tumors in the nasal cavity or lung (SCHEER 2021).

Polycyclic aromatic hydrocarbons (PAHs)

Around twenty polycyclic aromatic hydrocarbons (PAHs) have been identified mainly in the emissions. This is not surprising since these substances are typical products of incomplete combustion (WHO 2021)No. 1029. Some components may break down thermally when using electronic cigarettes and heated tobacco, forming PAHs. Regarding their potential health impact, many of the PAHs found in Erreur ! Source du renvoi introuvable. are presumed human carcinogens (group 1B) according to their CLP classification such as benzo(a)anthracene, dibenz(a,h)pyrene, chrysene, or even dibenz(a,h) anthracene. This is supported by the Agency for Toxic Substances and Disease Registry (ATSDR) which underlines that the most significant endpoint of PAH is cancer; although other effects involving PAH are described including pulmonary chronic toxicity or mutagenicity (ATSDR 2023). Indeed, several PAHs including benzo(a)pyrene, dibenz(a,i)pyrene, and dibenz(a,l)pyrene have a mutagenic potential based on their CLP classification.

Phenolic compounds

A dozen phenols are present in both types of products but have different origins. For HTPs, they originate from the pyrolysis of tobacco (Uguna et al., 2022)and that IQOS and potentially other heated tobacco products (HTPs, whereas for electronic cigarettes, their formation depends on factors such as the PG:VG ratio, power, and the duration of a puff (El-Hage et al. 2020). Cresols (o-, m-, and p-) are classified as possible human carcinogens (Group C) by the US EPA. Catechol is considered a probable human carcinogen and a possible mutagen (CLP group 1B and 2). Phenol is also classified as a possible mutagen for humans by CLP classification (Group 2), and resorcinol is an endocrine disruptor (BKH-DHI Category 1). These substances also possess other toxic effects. For example, cresols and resorcinol are respiratory irritants (HSDB 2023a).

Metals and metalloids

About ten metals and metalloids are detectable in the emissions of both products, notably arsenic, cobalt, lead, mercury, and selenium. Nicotiana tabacum, the tobacco plant, exhibits the capacity to accumulate metals and is occasionally employed for remediation purposes in contaminated soils (Bernhard et al., 2005)but can also destroy health when the concentration is not within the physiologically favourable range. Cigarette smoking interferes with the carefully controlled metal homeostasis of the human body. This review focuses on the consequences of metal delivery to the human body by cigarette smoking and discusses the body’s responses. The metal content of tobacco plants, smoke, the circulation, and various organs is discussed. Finally, we link individual cigarette smoke contained metals to the genesis of human diseases.”,”container-title”:”IUBMB Life”,”DOI”:”10 .1080/15216540500459667”,”ISSN”:”1521-6551”,”issue”:”12”,”language”:”en”,”note”:”_eprint: https:// onlinelibrary.wiley.com/doi/pdf/10.1080/15216540500459667”,”page”:”805-809”,”source”:”Wiley Online Library”,”title”:”Metals in cigarette smoke”,”volume”:”57”,”author”:[{“family”:”Bernhard”,”given”:”David”},{“family”:”Rossmann”,”given”:”Andrea”},{“family”:”Wick”,”given”:”Georg”}],”issued”:{“date-parts”:[[“2005”]]}}}],”schema”:”https://github.com/citation-style-language/schema/raw/ master/csl-citation.json”} . The presence of metals in HTP emissions may, therefore, be attributed, in part, to the utilization of tobacco cultivated in soil with pre-existing metal contamination. In the case of electronic cigarettes, these metals such as beryllium, cadmium, chromium, and nickel, may originate directly from the device’s components. For instance, nickel and chromium are principal constituents of coils commonly employed in electronic cigarettes. Arsenic, on the other hand, is sometimes present in e-liquids and can thus also be an impurity arising from the e-liquid manufacturing process.

The mentioned metals all pose significant hazards: arsenic, beryllium, cadmium, and chromium are classified as carcinogenic to humans (IARC group 1 or ACGIH group A1). Cobalt is considered probably carcinogenic to humans (IARC group 2A, CLP group 1B), while nickel and lead are classified as possible carcinogens to humans (IARC group 2B). Several of these metals are also classified as mutagenic or toxic to reproduction by the CLP classification. Furthermore, these metals show other toxic effects; for instance, lead is notably known for its toxicity to the central nervous system (HSDB 2023), arsenic is hemotoxic and hepatotoxic (ATSDR 2007), and cadmium is a respiratory irritant (ATSDR 2012).

Tobacco-related substances found in HTPs

Carbon disulphide

Carbon disulfide is a compound that naturally forms during complex chemical reactions that occur during the tobacco combustion process. Unlike electronic cigarettes which do not contain tobacco, it is common to detect carbon disulfide in the emissions of HTPs. This substance has been categorized as suspected toxic to reproduction (Repr. 2) by CLP classification and is known for specific target organ toxicity after repeated exposure (STOT RE 1). Additionally, it is linked to various health issues including coronary heart disease, retinal angiopathy, color perception issues, effects on peripheral nerves, psychophysiological effects, morphological and other effects on the central nervous system (HSDB 2023b).

Titanium dioxide

Titanium dioxide (TiO2) is included in the list of priority additives as laid down in the Commission Implementing Decision (EU) 2016/787[2]. This substance, found in HTP, is not directly added to the tobacco as it is applied to the filter material and to the paper as a whitening agent. In 2020, the European Commission (EC) classified titanium dioxide as a category 2 carcinogen according to the CLP regulation. It’s important to note that this decision has been the subject of numerous disputes leading to the revocation of the harmonised classification and labelling of titanium dioxide by the General Court of the European Union in 2022[3]. The main argument is that the requirement to base the classification of a carcinogenic substance on reliable and acceptable studies was not satisfied.

Mixture of substances

It is interesting to note that more hazardeous substances were identified in the emissions (n=111), collected via a literature review, than in the ingredients declared by the manufacturers (n=39), for these two products. This may be explained, by two reasons, the first is linked to the existing regulations (Directive no. 2014/40/EU) requiring manufacturers to report ingredients but not emissions. The second explanation could be that heating is inherent with the use of these two products: substances may decompose during heating creating new substances. These may react with other constituents, further increasing the chemical complexity of the aerosol. Indeed, some ingredients are inherently present but heating and mixing ingredients can cause a whole range of emissions. For example, several substances are derived from the degradation of propylene glycol (PG) and vegetable glycerine (VG, also known as glycerol), which are added as humectants in HTPs and as carrier substances in e-liquids (see Figure 1).

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[2] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016D0787&from=EN
[3] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:62020TJ0279

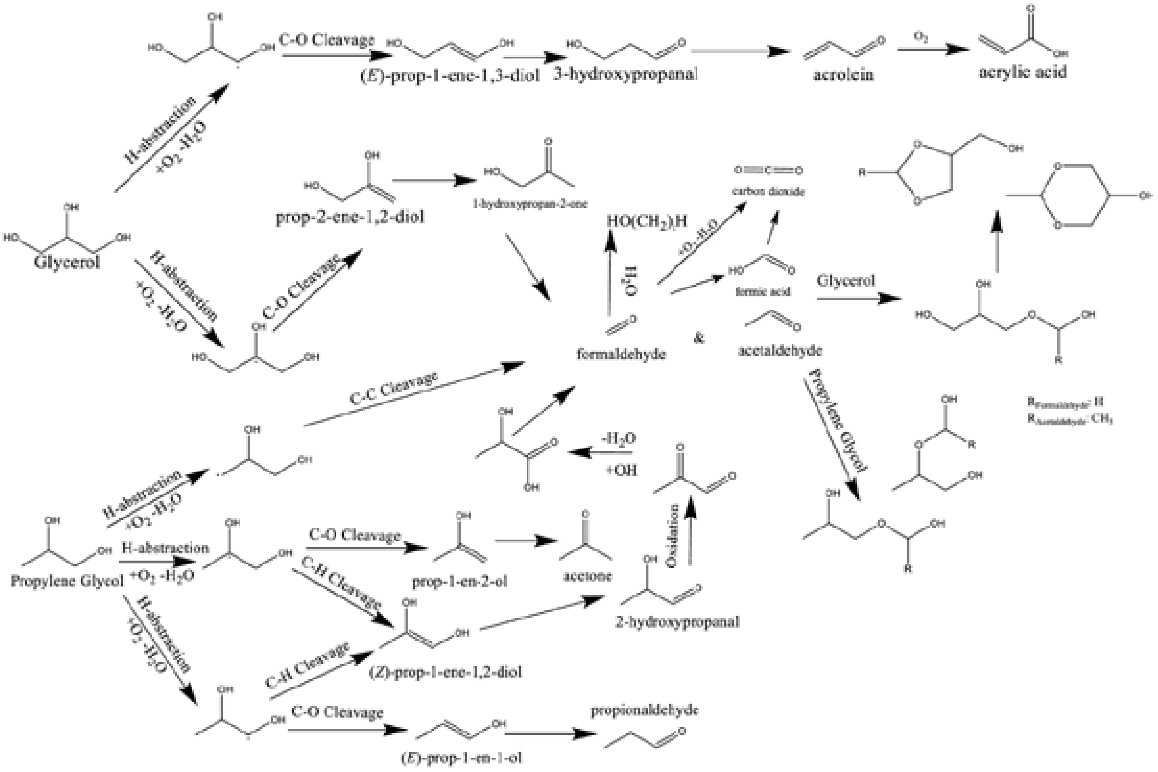

Figure 1: Degradation products of propylene glycol and glycerol at low temperatures (Jaegers et al. 2021)such thermochemical conversions are reported to occur between 300 and 400 °C. Herein, the low-temperature thermal degradation of propylene glycol and glycerol constituents of e-cigarette vapors are explored for the first time by natural abundance 13C NMR and 1H NMR, enabling in situ detection of intact molecules from decomposition. The results demonstrate that the degradation of electronic nicotine delivery system (ENDS.

PG and VG are the basic ingredients of the e-liquid and account for around 80% of the dilution support. However, the PG:VG ratio varies between e-liquids. It is interesting to note that, according to the BVA survey carried out for the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in 2020, 44% of French users use a PG:VG ratio with more propylene glycol and 40% use a 50:50 PG:VG ratio (Anses 2022). A PG:VG ratio of 20:80 would produce more acrolein than a 50:50 ratio according to Figure 1. It's important to point out that this issue is not specific to e-cigarettes because, as mentioned previously, PG and VG are also found in heated tobacco as they are used as humectants.

Besides the presence of a combination of ingredients, many parameters linked to device properties and user behaviour can influence the composition of the resulting emissions of e-cigarette. Indeed, there is a wide variety of e-cigarette devices with multiple options, such as adjustment of power and coil design. For heated tobacco products, there is a limited number of devices and few or no options for adjustment. These parameters will be detailed in the following section of the report.

II. Device properties

Background

The basic components of e-cigarettes include a battery that provides the electric current to the e-cigarette, an atomizer and a cartridge containing the e-liquid. The battery may be re-chargeable. The atomizer contains the coil or coils (heating element). The function of the coil(s) is to heat the e-liquid to create the aerosol that can be inhaled. Heating of the e-liquid can lead to thermal decomposition of the e-liquid constituents and/or induce formation of new compounds, depending on the temperature, chemical composition of the e-liquid, and duration of the heating (NAS 2018). The decomposition products that can be formed and transferred to the inhalable aerosol, may possess altered toxicity compared with their parent compounds. Constituents that have been identified in the aerosols that may not be directly derived from the e-liquid, include metals and silicate particles that may add to the toxicity of the inhaled e-liquid vapor (SCHEER, 2021).

The e-liquid is usually brought in contact with the coil through a wick, commonly made of silica, cotton, or ceramic materials (Omaiye et al., 2021). The e-liquid is contained in a cartridge or tank, which may be refillable or exchangeable. The manufacturers of e-cigarettes may change several of the components of the e-cigarette, and thereby possibly affect the amount and composition of the inhalable aerosol.

There are a several different coils on the market. These may be of different alloys. A study that investigated cartomizer style e-cigarettes, that were manufactured between 2011 and 2017, reported that nichrome (nickel, chromium) was the most used alloy (Williams et al., 2019). Other alloys reported are Elinvar (chromium, iron, nickel), Invar (iron, nickel), and Kanthal (aluminum, chromium, iron). A more recent study on 11 POD based e-cigarette devices reported that most coils were of Elinvar alloy (Omaiye et al., 2021). Some e-cigarette types enable the users to change the coil(s) themselves.

In some atomizers, the coil may be placed on the top (top coil) and fed with e-liquid through the wick by capillary forces, whereas bottom coils are fed through the wick by both gravity and capillary forces (Robinson et al., 2018). To avoid dry puffing, an important feature of the wick is to deliver e-liquid to the coils at the same rate as e-liquids are vaporized.

The battery of an e-cigarette determines the possible voltages that the user may apply. The e-cigarettes are manufactured both as a fixed or variable voltage devices. If the voltage is increased and the resistance of the coil is constant, the current will increase. This will enable a more rapid increase in temperature of the coil and thereby the e-liquid.

As an example, for single coils from different manufacturers, both the alloy, the diameter and the length of the coil may differ. Thus, by a similar change in voltage, a different amount of energy may be available for heating and vaporization of the e-liquid. A comparison of emissions by just comparing a change in volt is therefore not feasible. The amount of energy transferred from the coil surface area to the liquid, is known as heat flux or watt density. Two coils may deliver the same amount of energy/ watts, however, the surface area of the coil may differ. The one with a smaller surface area may achieve a higher temperature and thus higher heat flux. For direct comparison of emissions as a function of the applied watt or volt, the surface area and properties of the coil must be known. Soulet and co-workers (2021) showed that the coil resistance was lower for e-cigarette devices with higher recommended watt (to avoid overheating/dry puffs). In Appendix IV some basic units in electricity are explained in more detail.

There are also other factors reported to affect the coil temperature. Sufficient transport of e-liquid to the coil has been reported to be important to avoid high temperatures. Chen and co-workers (2018) observed that the coil temperature in the absence of e-liquid, increased linearly with increasing watt, and peak temperature of up to 1008°C was measured. However, if the coils were submerged in e-liquid, the peak coil temperature was under the boiling point of propylene glycol of 188°C. Heterogeneity in the temperature along the coil has also been observed, and the accuracy of the temperature control mode of some e-cigarettes, measured by deviation from the set temperature has been observed (Dibaj et al., 2018). The coil temperature will also be affected by the airflow, the amount of air drawn by the users. A higher airflow has been shown to reduce coil temperature, although the magnitude of the reduction may vary according to brand/design (construction) of the atomizer (Zhao et al., 2016).

Number of studies identified

After screening 6047 abstracts, we identified 275 articles, which could be relevant for the systematic review. After screening on abstract, we excluded 193 studies that did not fulfil the inclusion criteria after evaluation on the full text. Finally, 79 studies were included in the report and assessed for Risk of Bias (RoB) (Erreur ! Source du renvoi introuvable.Erreur ! Source du renvoi introuvable.).

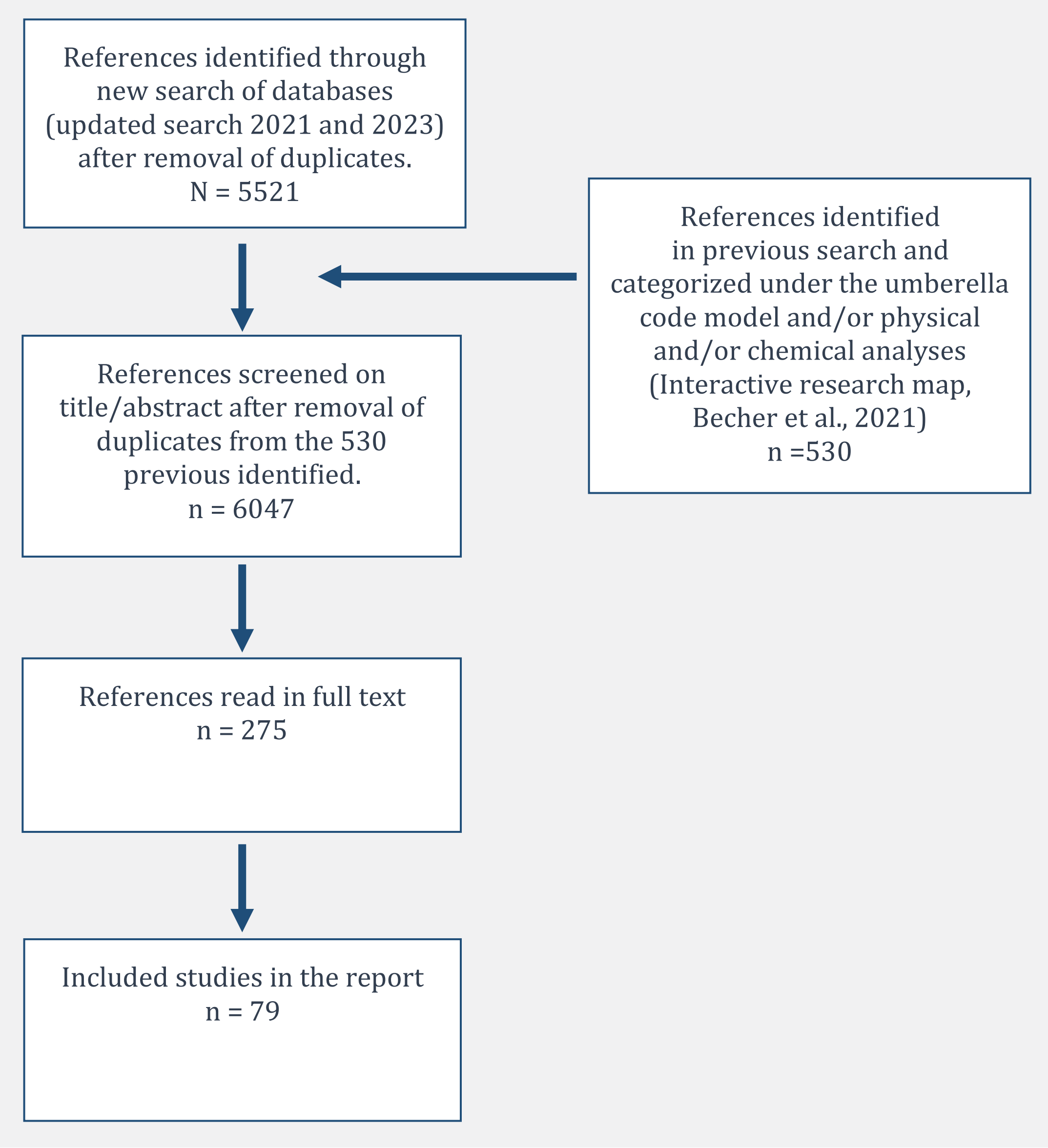

Figure 2: PRISMA flow diagram for device properties.

The identified studies eligible for RoB assessment are summarized in the four categories as shown in Appendix V - Studies eligible for RoB assessment and number of included studies after the RoB assessment. The outcome of the RoB assessment are shown as Excel file in a Supplementary document. Meta-analysis was not performed for any outcome due to reported differences in e-cigarette device properties, e-liquids and puffing topography.

Properties related changes in watt, ohm, volt or temperature and impact on emissions

E-liquid consumption and particles size and mass distribution in the aerosol

E-liquid consumed

Nine studies were included for GRADE assessment that investigated the amount of e-liquid consumed (Appendix IV, Table 1Erreur ! Source du renvoi introuvable.). The specific details on watt, ohm, temperature and e-liquid consumed are presented in Table 2 of Appendix IV. E-liquid consumed as a function of watt is presented graphically in Figure 3. All of the studies showed an increase in e-liquid consumption (based on weight difference before and after vaping) as a function of increasing watt, volt or temperature. All included studies on e-liquid consumption were observational studies, no randomized studies were identified. Our certainty in the effect, increase in e-liquid consumption as a function of watt, was upgraded from low to moderate certainty due to the consistent dose-response relationship (Appendix VI).

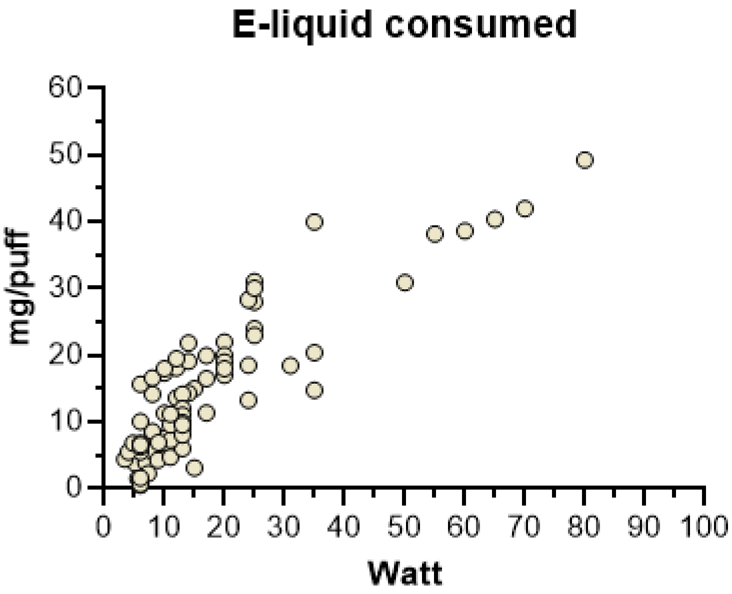

Figure 3. Amount of e-liquid consumed per puff with increasing watt. The data is based on the seven studies in Table 2 of Appendix IV.

Particle mass on filter

Eight studies were included that investigated the total deposition of particulate mass on a filter as a function of watt, volt or temperature (Appendix IV, Table 3). The specific details on watt, ohm, temperature (if given), e-liquid used and the amount particulate mass collected are presented in Table 4 of Appendix IV. All of the studies reported an increase in the mass of particulate matter as a function of increasing watt, volt or temperature.

Gravimetrically derived particle size distribution

Gravimetrical measurement of particles enable measurement of the mass size distribution of particles emitted from the e-cigaretttes. Seven studies identified used cascade impactors to investigate the mass particle size distribution. The specific details on watt, ohm, temperature (if given), e-liquid used, the amount of different fractions of particulate mass collected (if given) in addition to the specific results reported for each study, are presented in Table 5 of Appendix IV. Four of the identified studies reported on mass median aerodynamic diameter (MMAD). Two of the studies reported no statistical significant effect on MMAD as a function of the volt, ohm or watt investigated. However, two studies reported an increase in MMAD as a function of watt. The two studies (Ranpara et al., 2021, Mulder et al., 2019) that reported no significant effect investigated a relatively narrow watt range from 6.5 W to 7.5 W and 8.4 W to 12.32 W respectively, which may explain the findings. The other three studies identified, reported on mass change for the different particle size fractions: ultrafine particulate fraction (particles < 0.1 µm), fine particulate fraction (0.1-1 µm) and coarse particulate fraction (> 1 µm). One of the studies reported an increase in the total particulate mass with increasing volt applied. The mass was dominated by the fine particulate fraction for all voltages investigated. The latter finding was also reported in the study by Marocco et al., 2022. One of the other studies identified, investigated three different atomizers at either 200°C or 300°C. The authors reported an increase in the different particulate mass fractions as a function of temperature for some combinations of PG:VG ratios and atomizers type.

Real-time measurement of particle size distribution

Real time measurements of particles enable concomitant measurement of particle numbers and particle size distribution immediately after the formation. Eight studies were identified that investigated the real time particle size distributions and or number of particles as a function of a change in volt, watt, temperature, or changes in resistance. The specific details on watt, ohm, temperature and e-liquid used, the size range and number of particles generated in addition to the specific results reported for each study, are presented in Table 6 of Appendix IV. A bimodal or trimodal particle size distributions was reported (Dibaji et al, 2022, Floyd et al., 2018, Zhao et al.,2017). Some of the identified studies reported on changes in particle size and, or particle size fractions (Floyd et al, 2018, Lechasseur et al., 2019, Marocco et al., 2022, Son et al., 2020, Zhao et al.,2018), and some studies on changes in total particle number concentration and, or particle concentration for different particle size fractions (Dibaji et al., 2022, Ganguly et al., 2020, Marocco et al., 2022, Son et al., 2020) as a function of an increase in volt, watt or temperature. In general, the results indicated an increase in particle number and size with increasing power applied. An increase in power may increase the amount of e-liquid vaporized. This may enable more liquid to form particles that may condensate to form larger particles (Floyd et al.,2018). Thus, an increase in power may reduce the number of particles in the ultrafine fraction and increase the number of larger particles. Due to variability in methodology applied, different devices and e-liquids investigated, which are properties that may affect the particle size distribution, a precise range for the different modes and particle number concentrations are challenging to predict, as shown by Dibaji et al, 2022.

Particle size, mass related to other factors

Puff number, coil aging

Three studies were included that investigated how increasing puff numbers (coil aging) may affect the particle size and mass of the aerosol. Heterogeneity in how an increase in puff number could affect the particle size and mass, both within and between brands were observed (Appendix IV, Table 7). Two of the studies identified reported on the JUUL device. The studies on JUUL, from the same group of authors, reported different results with increasing puff fraction. One of these studies reported an increase in particle concentrations, whereas the other reported a decrease in particle mass and concentration with increasing puff fraction. For the other pod device investigated, the total particular matter was fairly similar up to when the coil started to fail. Coil failure may increase the resistance of the coil and cause an increase in temperature. The study by Zhang and co-workers (2023) investigated different wattages and coil resistance by using a mod type e-cigarette in addition to the JUUL device. The authors observed no clear trend for the mod-type e-cigarette in relation to increasing number of puffs and possible effects on particle concentration and mass.

Reinserting the pod and direct dripping

One study investigated the effect of removing and re-inserting the pod during a 10 puff cycle (Appendix IV, Table 8). Without re-inserting the pod, the level of PM2.5 was highest initially, and leveled off after 5 puffs. Removing and re-inserting the pod kept the PM2.5 level at a higher concentration than without removing and re-inserting the pod. Another study investigated the total particular matter as a function of interdrip interval (the interval between dripping e-liquid directly on the coil) under a direct dripping regime (Appendix IV, Table 9). The authors reported that when increasing the interdrip interval, a lower level of total particulate matter (TPM) over four puffs was collected.

Nicotine and nicotyrine

Concentration of nicotine in aerosol

We identified 12 studies investigating the aerosol nicotine concentrations as a function of changes in watt or volt (Appendix IV, Table 10). The wattage range was from 3 to 75 watts. All studies reported a wattage dependent increase in the amount of nicotine per puff. However, similar amounts of nicotine (µg) per mg mass vaped were observed (Table 11 of Appendix IV; Figure 4). This indicates that transfer of nicotine from the e-liquid to the aerosol occurs at a similar rate as the solvents. Thus, the user may inhale a larger amount of nicotine with increased wattage, as a larger amount of e-liquid is aerolized with increasing wattage.

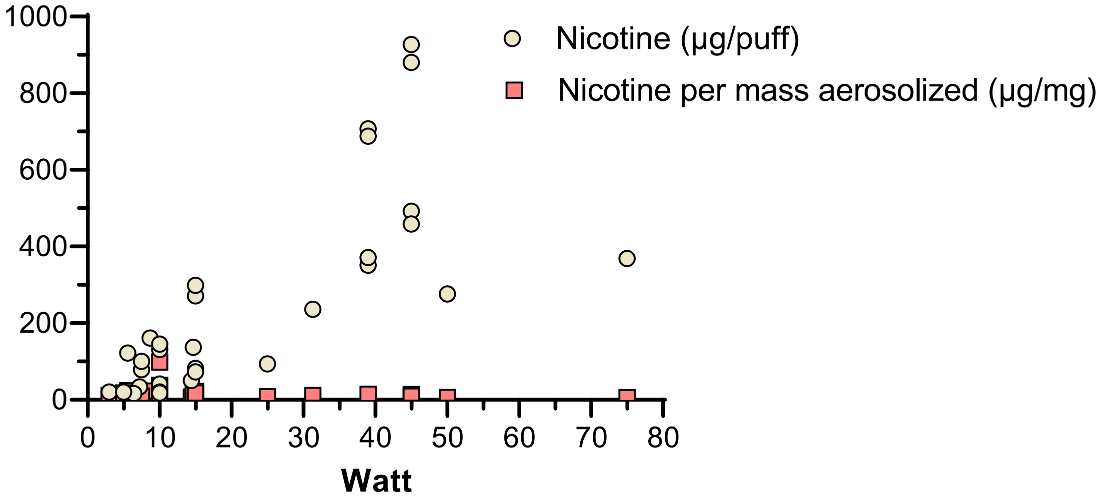

Figure 4: Concentration of nicotine in the aerosol per puff and per mass e-liquid aerosolized as a function of watt. The data is from the 7 studies reporting nicotine per mass aerosolized as a function of watt (Table 11 of Appendix IV).

Nicotine concentration in aerosol from direct dripping

Direct dripping is a practice to generate the e-liquid aerosol by dripping the e-liquid directly onto the coil before inhalation. This practice enables the user to modify the amount of e-liquid applied to the coil, and how many puffs the user may take before dripping on fresh e-liquid. The study by Talih and co-workers (2016) showed that the interdrip interval, i.e. the number of puffs between directly applying new e-liquid onto the coil, affected the nicotine concentration in the aerosol (Appendix IV, Table 12). The authors reported a reduced nicotine concentration after 15 puffs, when the interdrip interval increased from two to four. This may be explained by that less e-liquid is available to evaporate at later puffs, when the inter drip interval is increased.

Nicotyrine

Two of the included studies investigated the amount of nicotyrine formed as a function of watt or volt. Nicotyrine is an oxidation, dehydrogenation product of nicotine, which has been described to inhibit CYP 450 enzymes responsible for nicotine metabolism (Abramovitz et al., 2015). Thus, nicotyrine may prolong the clearance time of nicotine. The study by Son and co-workers (2018) reported that the amount of nicotyrine available for inhalation increased with increasing watt applied. However, the amount of nicotyrine relative to the mass of e-liquid aerolized at the watts investigated, did not increase, the latter was also reported by Sleimann and co-workers (2016). Detail of the studies are presented in Table 13 of Appendix IV.

Formation of nicotine adducts

One study was included that identified constituents in the e-cigarette aerosol by an untargeted chemical analysis. The authors observed formation of nicotine – propylene glycol (NIC-PG) adducts, and investigated the amount formed as a function of increased watt. The authors were not able to directly quantify the amount of NIC-PG adducts formed, due to lack of a standard. However, they reported an increase in the ratio between NIC-PG and nicotine with increasing watt applied. Details of the study are presented in Table 14 of Appendix IV.

Volatile organic compounds (VOCs) identified in aerosolized e-liquid

We identified 27 studies investigating the VOC in aerosolized e-liquid as a function of changes in watt or volt (Appendix IV, Table 15). Volatile organic compounds identified in the aerosolized e-liquid include the solvents propylene glycol (PG) and vegetable glycerol (VG) and different flavouring compounds. In addition, impurities in the e-liquid and formation of degradation products caused by heating of the e-liquid by the coil, such as formaldehyde and acetaldehyde, have been identified.

Three of the most frequent VOCs that were reported in the e-cigarette aerosols were formaldehyde, acetaldehyde and acrolein. These substances are known degradation products from glycerol and propylene glycol. Other VOCs that were identified include more than 30 different substances (Appendix IV, Table 15), which included various carbonyls and phenols. The concentrations of VOCs that were measured in the aerosols in the different studies showed large variations. The general observation within each study was that the concentrations of generated VOCs measured in the aerosols increased as a function of power (watt) and temperature.

As reported above, an increase in wattage while holding the other parameters constant, will also increase the amount of e-liquid aerolized. In Table 16 of Appendix IV and Figure 5, we provide as an example the amount of formaldehyde formed per mg mass vaped. This to elucidate if there was a constant rate of formaldehyde formed per mass consumed or if this ratio changed with increasing wattage. In general, there was no indication that higher wattage increased the formation of formaldehyde per mass consumed. Table 17 and Table 18 of Appendix IV show the amount of acetaldehyde and acrolein formed per mg mass vaped, showing similar trends as for formaldehyde.

It appeared that there was a correlation between the surface area of the coil, e-liquid consumed and thereby emission of VOCs per puff. An explanation for this may be that a larger contact area between the coil and the e-liquid may enable more energy to heat and vaporize the e-liquid without overheating the coil.

In some of the studies it was, however, observed that an increase in wattage also induced an increase in the formation of formaldehyde per unit mass of generated aerosols (Appendix IV, Table 16). At a constant resistance (ohm), an increase in wattage implies that more energy may be transferred to the coil resulting in higher coil temperatures. In some e-cigarettes, the wattage may be increased above the capacity of the coil, causing the temperature of the coil to increase to the extent that film boiling occurs, resulting in increased decomposition of solvents (and increased formation of VOCs, like formaldehyde). In addition, increased formation of decomposition products may be caused by so-called dry puffing. This occurs when the rate of evaporation exceeds the capacity of the wick to deliver e-liquid to the coil, resulting in increased coil temperatures. This may be followed by an increased thermal decomposition of the e-liquid into various decomposition products such as formaldehyde and acrolein. Ideally, the device should be designed so that dry puffing is avoided and the power controlled so that the heat transfer is below the critical heat flux.

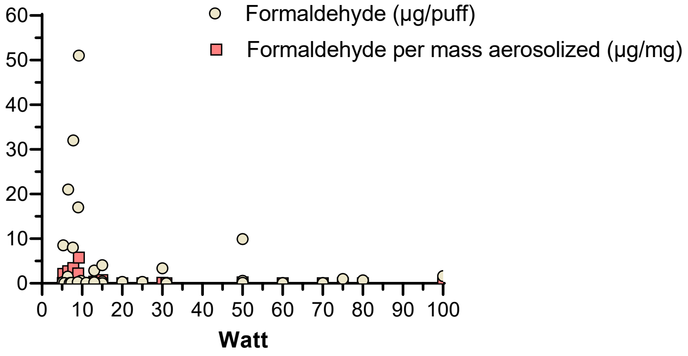

Figure 5: Concentration of formaldehyde in the aerosol per puff and per mass e-liquid aerosolized as a function of watt. The data is from the 3 studies reporting the formaldehyde concentration per mass aerosolized as a function of watt (Appendix IV, Table 15)

VOC emissions in relation to other properties than changes in watt

Airhole opening

Some e-cigarettes may let the users adjust the air hole opening. Thus, the user may adjust the ease at which the amount of air is drawn through the e-cigarette. When using an e-cigarette, a pressure drop develops when the user inhales. The pressure drop has for some e-cigarettes shown a good correlation with air hole diameter of the e-cigarette, although high variability was reported among the e-cigarettes investigated (Williams and Talbot, 2011). We identified one study investigating airhole opening and VOC formation (Cancelada et al 2021, Table 19 of Appendix IV). The authors reported a decrease in formaldehyde concentrations when the air hole opening increased, keeping the puff volume constant. It was suggested that a cooling effect due to increased air hole opening resulted in less carbonyl formation.

Puff number and coil aging

We identified one study investigating the impact of puff numbers and coil aging on VOC formation. Results showed that if the coil is used for a high number of puffs, formation of formaldehyde and acetaldehyde may increase (Goto et al., 2021, Table 19 of Appendix IV). The authors observed that the coils turned black after extended use, wich may be an indication oxidation of the coil leading to coil malfunction.

Direct dripping

We identified one study investigating the impact of direct dripping on VOC formation (Talih et al., 2016, Table 19 of Appendix IV). Some users may drip e-liquid directly on the coil before inhalation of the aerosol. The temperature of the coil may thus increase as liquid evaporates without replenish. More VOCs may then be generated due to increased coil temperature as discussed above. The authors observed that the temperature of the coil increased with an interdrip interval of 3 and 4, and observed an increased amount of VOCs generated at the elevated temperatures (Talih et al., 2016).

Reactive Oxygen Species (ROS) formation in relation to watt, volt, temperature and resistance

Four studies on ROS in aerosols from e-cigarettes as a function of changes in watt or volt were included (Appendix IV, Table 20).

One study used the dichloro-dihydro-fluorescein diacetate (DCFH-DA) method, a fluorescence based method used to assess ROS formation. The study reported an increase in ROS formation with increasing watt both for the supra-ohm device and the sub-ohm device tested (Haddad et al., 2018). An increase in ROS per ml e-liquid consumed was only observed at the highest wattages for both devices (11 W and 200 W respectively).

Another study (Son et al., 2019) reported a watt dependent increase in ROS formation (*OH) measured as 2-hydroxyterephthalic acid (2-OHTA) whereas another study reported a watt dependent increase in ROS concentration per puff using the Trolox method (Zhao et al., 2018b). The amount of H2O2 as well as its percentage increased with increasing voltage.

One study using EPR (electron paramagnetic resonance) spin trap and lipid peroxidation (MDA-eq) method reported higher formation of free radicals per gram of solvent (75:25 PG/GLY solution) when increasing the temperatures from 200□ to 300□ and the wattage from 25 to 50W (Bitzer et al., 2018a). The results also indicate that free radicals can be formed at lower temperature and power (100□ and 10W).

In general, an increase in ROS with increasing watt or temperature was observed. However, ROS formation may depend on the e-liquid composition. It is uncertain if the increase in ROS may be due to a concomitant increase in aerosolized e-liquid as this was not reported.

ROS formation as a function of changing the air-hole opening

Adjustable air holes determines the ease at which the amount of air is drawn through the e-cigarette. E-cigarettes or atomizers may come with both fixed or adjustable air holes diameters. The study by Son and co-workers (2019) investigated how the air hole diameter affected the levels of hydroxyradicals in the aerosol (Appendix IV, Table 21). Numeric results were only reported for the VG based and the PG:VG based e-liquids, indicating an increase of approximately 14% and 119 % respectively when comparing an air hole diameter of 1 mm with that of 2 mm at 31.3 watt. Taken together, the levels of hydroxyradicals may be affected by air hole diameter, e-liquid composition and wattage.

Metal concentrations as a function of changes in watt

Three studies on metals identified in the emissions from e-cigarettes as a function of changes in watt were included (Appendix IV, Table 22). A range of different metals were identified in aerosols from e-cigarettes. The studies by Kapambia and co-workers (2022) and Zhao and co-workers (2019) showed that changes in the watt may change the metal element composition of the aerosol (Appendix IV, Table 23). Kapiamba is not listed in the Table 23 of Appendix IV since their results/ data are only presented graphically. However, both an increase and decrease were reported for some metal elements, thus not all metal elements were reported to increase as a function of increasing watt. In the study by Zhao and co-workers (2019) an increase in the metal elemental composition of the aerosol was most pronounced when comparing 20 watt to either 40 or 80 watt. Some of the elements were found in relatively high concentrations, such as nickel (Ni), copper (Cu), zinc (Zn), tin (Sn), iron (Fe) and lead (Pb) (Appendix IV, Table 20).

The metallic elements detected in the aerosols from the e-cigarettes may have a range of different sources (Williams et al., 2019). In addition to impurities in the e-liquid itself, there are several metallic parts in the device that may be exposed to the e-liquid. These are the coil, wires connecting the battery to the coil, and the soldering that connect wires to the coil. The metalloid silicon may be derived from the wick, or the sheat used for isolation. Copper may be derived from brass clamps, and the wire connecting the electric circuit to the coil. Lead and tin may be derived from soldering joint, often made of various alloys of tin with different amount of lead or trace amount of lead, connecting the different part of the e-cigarette. The relatively high levels of lead in the e-liquid in the study by Zhao et al. (2019) may therefore come from the solder. The variation in metals measured in the aerosol between e-cigarettes may thus partly be explained by the different alloys used for the contruction of e-cigarettes, the e-liquid used and the power applied.

Metal concentrations as a function of the number of puffs

Four studies were identified that investigated changes in metal concentrations in the aerosols as a function of the number of puffs as a measure for coil aging (Appendix IV, Table 24). All studies included reported that the number of puffs affected the metal composition of the aerosol, but with high variability in quantity as a function of coil aging and no consistent trends. Both an increase and a decrease in metal emissions , as well as no changes are reported as a function of coil aging.

Polycyclic aromatic hydrocarbons in relation to watt, volt, temperature and resistance

One study (Dusatoir et al., 2021) reported on PAH content in emissions from e-cigarettes as a function of changes in watt (18 or 30 W, Table 25 of Appendix IV). Twentytwo different PAHs were identified in the aerosol generated at each wattage investigated. Most of the PAHs were detected at concentrations less than 2pg/puff, whereas naphthalene, phenantrene, pyrene and fluoroanthrene were detected at concentrations ranging from approximately 10 to 90 pg/puff. No significant difference in sum of total PAH content was reported between the two wattages. At 30 W, some compounds, such as dibenzo(a,l)pyrene, dibenzo(a,h)anthracene and dibenzo(a,e)pyrene were identified that were not found at 18 W, but at very low concentrations (< 1 pg/puff). No statistical analysis was, however, reported for single PAH compounds. The sources of the analyzed PAHs were not identified, but could be derived from the e-liquid.

Other emissions related to watt, ohm and volt not defined in the protocol

Carbonmonoxide

Four of the included studies investigated the amount of carbon monoxide (CO) formed in relation to changes in watt or volt (Appendix IV, Table 26). Three of the studies, those using > 15 W reported an increase in CO concentrations as a function of wattage applied.

Chloropropanols

We included one study (Moser et al., 2019) that investigated the amount of different chloropropanols, chlorinated degradation products of the chlorine containing artificial sweetener sucralose, using an e-cigarette at different temperatures but at a constant watt. There were no marked changes in the amount of chloropropanols in the aerosol as a function of increasing temperature. For study specific results see Table 27 of Appendix IV.

Impact of coil and other metal parts on emissions

Impact of coil

Two studies were included on the impact of coil materials and other parts on emissions (Appendix IV, Table 28). The study by El-Hellani (2019) provides insight into the role of coil material and coil configuration, such as number of wraps of the coil, diameter of the coil and surface area (Appendix IV, Table 28). Although high standard deviations were reported for the CO measurements, there was a trend that the number of wraps of the coil affected CO emission, as reported for the Kanthal coil with 10 wraps compared to that with 13 wraps, and same surface area. In addition, the authors observed a trend that the coil alloy may affect the CO produced during use.

Impact of other metal parts

Williams and co-workers (2015) reported high concentrations of tin in the aerosol, which could be attributed to the solder joints (Appendix IV, Table 28). Tin coating on copper wires also contributed to tin in the aerosol. The coil configuration has been reported to affect the temperature of the coil both without and in the presence of e-liquids (Mulder et al., 2020). However, the number of coil wraps around the wick has been suggested to affect the thermal energy transfer, where a greater number of wrappings will enable a more homogenous energy distribution along the wick, which may prevent hot spots (high local temperatures) (Vreeke et al., 2020).

III. DIY practice

In total 421 articles were found matching the search keywords. After removal of duplicates, the search retrieved 184 items. Upon review of the article titles and abstracts, 212 articles were excluded due to irrelevance to the research questions. Examples are when DIY is mentioned (but not the direct cause) with poisonings of (pure) nicotine (refills) liquids, modifications of e-cigarette devices and in the context of vaping illegal substances.

Of the remaining 24 publications, two were conference abstracts and one full text was not available. The additional Google scholar search retrieved 18 relevant publications. A total of 39 articles were included in the discussion of the research questions. Figure 6 shows the PRISMA diagram that illustrates the steps that accompanied the selection process.

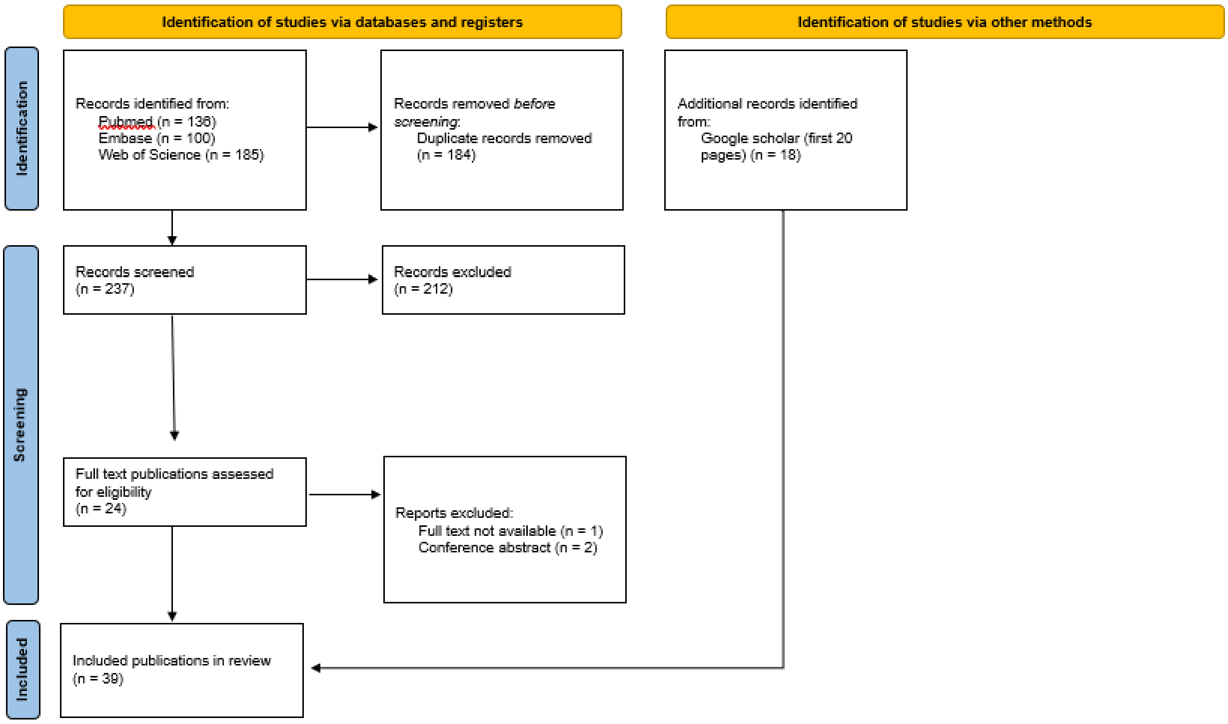

Figure 6: PRISMA flow diagram for DIY practice

The publications are grouped in 4 major topics: safety of DIY, motivations/behaviour of DIY users, chemical analysis of DIY liquids and regulatory context. The most investigated topic is about the motivations and behaviour of DIY e-liquid users, followed by chemical analysis of DIY e-liquid products and their safety (Figure 7).

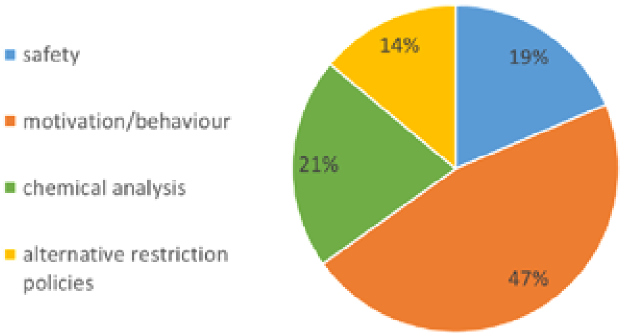

Figure 7: Major topics linked to the DIY practice.

Background

Do-It-Yourself (DIY) e-liquids, also known as homemade e-liquids are created by mixing different ingredients together. These ingredients are in general the same as in commercial e-liquids: propylene glycol (PG), vegetable glycerine (VG), nicotine and flavourings. Flavours are typically available in concentrated form (single flavour or mixtures of flavours) to be diluted.

Recipes for DIY e-liquids can be found from a variety of sources. Online communities and forums websites like Reddit, E-Cigarette Forum (ECF), and other vaping forums often have sections dedicated to DIY e-liquid creation (Wang et al. 2015). Also social media platforms like YouTube, Instagram, and Facebook have many users and groups that share recipes and instructional videos (Massey et al. 2021; Guy et al. 2019; Li, Ashley, et Popova 2022; Massey et al. 2020)used ENDS in the past 30 days, and had been using ENDS for more than 2 months. Some physical and online vape shops may provide basic recipes or mixing guidelines, especially those that sell DIY supplies. There are also vaping related apps, of these applications 35% (28/79) were intended to help mixing DIY e-liquids (Meacham, Vogel, et Thrul 2020). Meacham et al. found these applications in Google Play Store and investigated the purpose of vaping applications after Apple removed these from the App Store. Most vaping apps had features to help users continue vaping or maintain interest in vaping. Few apps were designed to help stop smoking or vaping (Meacham, Vogel, et Thrul 2020).

Records of practice

DIY e-liquid creation tends to be more popular among advanced vapers who have been using e-cigarettes for some time and it is generally considered a niche segment within the vaping community. DIY is seen as an important attribute of the specific vaping subculture which put itself against a 'mainstream' vaping culture, mostly identified by users who utilize the e-cigarette to quit smoking or to switch to a less hazardous alternative. The vaping subculture is more a lifestyle and the DIY ethos and customization is not only a hobby, it is part to express authenticity and expert knowledge (Tokle et Pedersen 2019; Thirlway 2023).

In Table 5 we summarized studies and surveys about the practice and motivations of e-cigarette users that make their own e-liquids.

With the convenience of pre-made e-liquids, and the fact that DIY e-liquid creation can be time-consuming, it's likely that e-cigarette users that make their own e-liquid represent a minority of overall e-cigarette users.

The first study reporting number of DIY e-liquid users was an online survey by Etter (2016). He conducted a study among e-cigarettes users (n= 1685) in France, US, Switzerland between 2012-2014, at that moment 11% reported to make their own e-liquids and 40% had ever mixed their own liquids (Etter 2016). More recently (2022), a survey in France conducted by ANSES reported that 48% of the participants (n = 1002) declared that they made their own e-liquid at least once in a while (Anses 2022b). In a study of Li et al., (2020) which interviewed 13 e-cigarettes users in 2013 to investigate modification of different aspects of ENDS found that more than half of the participants mentioned modifications to e-liquids such as refilling closed pods that are not meant by the manufacturer to be refilled, changing e-liquids with different flavours or nicotine levels, and producing their own by mixing different e-liquids or other substances (Li et al. 2020). These studies suggest that DIY practices occur more often than suspected of a niche e-cigarette users segment. The US based Hart et al. survey from 2021, showed that 17,5% of e-cigarette users (n = 1432) make their own e-liquid. In the same survey they have remarked that users who make their own liquid were 40% more likely to report E-cigarette or Vaping Use-Associated Lung Injury (EVALI)-like symptoms.

Data on the prevalence of DIY practices among e-cigarette users is currently too scarce to make any legitimate assumptions, but a trend towards an increase in DIY practices among e-cigarette users can be observed.

Table 5: Summary of studies and survey dealing with practice and motivations of DIY e-cigarette users.

	Year	Participants	Makes DIY	Fun/novelty	Reduce cost	Customization	Ingredient transparency	Tailored nicotine levels	
(Cox et al. 2019)	2017	41	100% (DIY was inclusion criteria)	92.7%	80.5%		48.8%	12.2%	
(Etter et al. 2016)	2012-2014	1685	40%		61%	50% (obtain better flavour) 22% (obtain better troat hit)		37% (reduce gradually nicotine intake) 30% (decrease concentration of nicotine) 5% (increase concentration of nicotine)	
(Hart et al. 2021)	2021	1432	17.5% (#250)						
(Record, Groznik, et Sussman 2023)	n.m.	4 (focus) 138 (qualitative)	100% (DIY was inclusion criteria)		X			X	29% has ever sold their mixed DIY e-liquid
(Li et al. 2020)	2013	13 (focus)	>50%		X	X (use of salts and additives- CBD & THC)		X (use of salts)	
(Massey et al. 2021)	2020	32 (focus)	n.m.			X (desired taste, adding cannabis products)		X (altering nicotine levels to manage physiological needs - using different levels at different times)	
(Balewska et Raciborski 2021)”plainCitation”:”(Balewska et Raciborski 2021	2020	a quantitative and qualitative analysis of Polish online forums and portals related to e-cigarettes	n.a.		11% of the comments	12% of comments			Some posts warned against possible dangers of using poor-quality ingredients miscalculating the proportions

DIY behaviour and motivations

The motivations to start and continue DIY practices can be summarized in five main reasons (Table 5).

- Cost savings: DIY e-liquids are perceived to be more cost-effective compared to commercially available e-liquids (Record, Groznik, et Sussman 2023; Li et al. 2020).
- Customization: DIY e-liquids allow vapers to have control their vaping experience. This customization appeals to individuals who prefer a specific flavour or want to obtain a certain throat hit (Etter 2016). This includes the addition of nicotine salts and additives such as cannabidiol (CBD) products (Massey et al. 2021; Li et al. 2020).
- Tailored nicotine levels: as part of the customization of DIY liquids, users can adjust the nicotine levels in their e-liquids to achieve their preferred nicotine strength or in some cases to circumvent the maximum concentration limit of the Tobacco Products Directive (TPD) (Ward et al. 2020; Cox et al. 2019)Article 20, implemented in Europe by May 2017, aimed to improve

safety for e-cigarette consumers, and prevent uptake among non-smokers, particularly young people. Before implementation, there were significant concerns from consumers, industry, and some in the scientific community about the potential negative impact of the TPD on people using e-cigarettes to remain abstinent from smoking. To date, there is limited evidence on how the TPD has affected consumers. This study aimed to add insight into how consumers perceived and experienced the regulations.\nMethods: Qualitative data, collected between March 2018 and March 2019, relating to participant views of the TPD were extracted from 160 interviews/extended surveys of e-cigarette consumers as part of a wider study into e-cigarette use trajectories (ECtra study.

- Fun and novelty: For many vapers, creating DIY e-liquids becomes a hobby and a creative outlet. It allows them to experiment, explore new recipes, and share them with others. For some, being a part of this community is a big part of the appeal (Record, Groznik, et Sussman 2023). Soule et al. have seen that during the COVID-19 pandemic e-cigarette users have spent more time on improving e-cigarette skills such as "perfecting" DIY e-liquid recipes as a means to pass the time (Soule et al. 2020).
- Ingredient transparency: By making their own e-liquids, users may perceive that they have full knowledge of the ingredients used (Cox et al. 2019).

These arguments are most often quoted when participants are asked about their motivations. The perceived cost benefits are identified as the most quoted motivation of DIY (Etter 2016; Anses 2022b; Cox et al. 2019). Record et al. have worked with a focus group to determine important factors to initiate and continue with DIY e-liquid mixing (Record, Groznik, et Sussman 2023). They have found that social influences (offline, person-to-person influences, friends) and online space are important for the initiation of DIY practice. These environmental factors are combined with personal sources of motivation such as curiosity and control of the e-liquid composition, especially nicotine content. Finally the behaviour motivators to continue or quit DIY e-liquid practice are associated with the perceived benefits (costs) and barriers. In this study, quality control was mentioned as a drawback of DIY practice, in which case commercial e-liquids were perceived to be of better quality. (Record, Groznik, et Sussman 2023).

Potential risks associated with DIY practice

In a survey of Massey et al. participants mention to have mixed liquids that tasted bad or caused physical illness (nausea) (Massey et al. 2021). Also Hart et al. found that participants who reported mixing their own e-liquid were 40% more likely to report EVALI-like symptoms and twofold more likely to report any symptoms (Hart et al. 2021). Although data about the safety of DIY e-liquids is limited, the literature review also revealed some specific health risks which are associated with the use of DIY e-liquids which are discussed here below.

Improper ingredient handling

DIY e-liquid mixing involves handling concentrated nicotine, flavourings, and other ingredients and is associated with leaking and spilling during use (Kyriakos et al. 2018). When handling pure or highly concentrated nicotine solutions during DIY e-liquid creation, there is a risk of accidental dermal nicotine exposure and subsequent poisoning due to the high transdermal absorption properties of nicotine (Maina et al. 2017; 2016).

Outside the EU and the regulation of the TPD, highly concentrated nicotine liquids (>20 mg/ml) can be used for DIY e-liquids. These come in concentrations of 100mg/ml or more and in volumes of 1000ml. It is reported that the risk of fatal outcome due to accidental ingestion is higher with these liquids compared with commercial available e-liquids (Morgan, Jones, et Kelso 2021)originally due to come into force on 1 January 2021. Additionally, the Therapeutic Goods Administration is in the process of rescheduling nicotine for use in e-fluids. We are concerned that the 270 000 daily vapers in Australia will purchase high concentrations of nicotine (≥100 mg/mL. Commercial e-liquids tend to use dropper dispensers, which make it difficult to deliver large volumes quickly. This may reduce the risk of accidental exposure for both adults and children. These can be directly compared to concentrated nicotine samples, which have open necks to allow the sample to be transferred using a syringe. This open neck design of the bottle could result in rapid exposure to large volumes of concentrated e-liquid through the oral or dermal routes. (Morgan, Jones, et Kelso 2021)originally due to come into force on 1 January 2021. Additionally, the Therapeutic Goods Administration is in the process of rescheduling nicotine for use in e-fluids. We are concerned that the 270 000 daily vapers in Australia will purchase high concentrations of nicotine (≥100 mg/mL.

The DIY practice might also be encouraged by social media platforms. Guy et al. reported some unorthodox use of DIY mixing in Youtube content. Such as unappropriated ways to test the quality of DIY liquids and using unqualified equipment for the preparation of DIY (Guy et al. 2019).

Attractiveness

The appeal of DIY e-liquids to certain users may be enhanced by the aspect of customisation which is inherent to the production of DIY e-liquids (Cox et al. 2019). This personalization enables users to tailor the e-liquid constituents to match their individual preferences, potentially optimizing the vaporization experience. The participants in the study of Cox et al. were long-term e-cigarette users, who had quit smoking and had no plans to stop vaping. DIY e-liquid mixing was a key factor enhancing their continued enjoyment of vaping (Cox et al. 2019).

There are also situational factors that might contribute to the attractiveness of DIY practices (Record, Groznik, et Sussman 2023). For example, the availability of online communities to share practices might encourage more engagement. It is important to be aware that these social media channels and apps don't always have age controls allowing anyone, also youth to learn about DIY ideas and approaches (Record, Groznik, et Sussman 2023).

The attractiveness of these DIY yourself products is also strongly correlated with the attractiveness of (characterizing) flavours. Soule et al. found that one of the reasons for the appeal of flavours in e-cigarettes is the ability to choose one's own unique flavour and the customizability by mixing one's own liquid (Soule et al. 2016). Schneller et al. also concluded from their surveys that there is evidence to suggest that the wide variety of flavours available and the freedom to mix and match flavours may maintain the use of e-cigarettes among adolescents and adults (Schneller et al. 2018). DIY practices may also affect the attractiveness of using flavourings in e-cigarettes.

There is still a paucity of studies investigating how modifications affect attractiveness and addiction. Research is needed to determine the potential effects on e-cigarette users who make their own e-liquids.

Ingredient quality and safety

The quality and safety of ingredients used in DIY e-liquids can vary. It is interesting to note that one of the motivations for DIY is the perceived control over the ingredients used and the quality of the e-liquid (Cox et al. 2019). While by some other users, the quality of ready to use products considered to be better than that of the DIY products (Record, Groznik, et Sussman 2023).

Besides products specifically designed for use in DIY e-liquids, it is possible that some flavourings used in DIY e-liquids may not be specifically intended for e-cigarette use. Some natural extracts and essences, such as vanilla extract and coffee extract, have been used to add flavour to DIY e-liquids[4]. In addition to extracts and oils, the addition of perishable foods such as apple and orange juice was mentioned by a participant in a focus group study (Massey et al. 2021). The aerosolization and inhalation of these aerosols are unknown and might introduce a potential hazard. However, this may also be the case for flavouring agents intended for e-cigarette use, most of them are safe for ingestion, but not necessarily for inhalation.

Some users may choose to add additional additives to their e-liquids, such as sweeteners, cooling agents (Leventhal et al. 2022)'Raspberry Ice', or other enhancers. Holt et al. mention the increased likelihood of higher ethanol levels in DIY e-liquids due to their use in flavourings, addition to dilute the liquid, to help dissolve other substances that are not miscible with typical carriers, or for intentional

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[4] https://www.reddit.com/r/DIY_eJuice/comments/2ly2k3/diy_coffee_extract_help/?rdt=58288&xpromo_edp=enabled
https://www.reddit.com/r/DIY_eJuice/comments/2161s8/regular_vanilla_extract/

consumption of ethanol (Holt, Poklis, et Peace 2021)"plainCitation":"(Holt, Poklis, et Peace 2021. Little is known about the toxicological effects of frequently inhaling ethanol. Leventhal et al. noticed the popularity of non-menthol synthetic cooling agents such as 'WS-23' in concentrated DIY formulations (Leventhal et al. 2022)'Raspberry Ice'. These concentrated cooling agents are often mixed with fruit- or dessert-flavored e-liquids to produce 'ice-flavoured' e-liquids. These are known to increase e-cigarette appeal and suppress nicotine's bitterness making nicotine-products more attractive. There are reports of tolerance towards the sensory attributes of these synthetic coolants (Leventhal et al. 2022)'Raspberry Ice'. As a result, users tend to augment the quantity of the coolant concentrate they mix into their e-cigarette solution to achieve the same effect. Thus high exposure to potental harmful components may be facilitated by the DIY possibility.

Ultimately, the endless possibilities of additives create the potential for misusing certain substances in home-made e-liquids. For example, some individuals experiment with adding illicit drugs or psychoactive substances, such as tetrahydrocannabinol (THC) or synthetic cannabinoids, to their e-liquids (Varlet 2016)these electronic devices have been introduced all around the world to support tobacco smoking cessation. Same potential harm reduction could be considered by cannabis vaping for marijuana smokers. However, the toxicities of liquids and aerosols remain under investigation because although the use of e-cigarettes is likely to be less harmful than traditional cigarette smoking, trace levels of contaminants have been identified. Simultaneously, other electronic devices, such as e-vaporisers, e-hookahs or e-pipes, have been developed and commercialised. Consequently, misuse of electronic devices has increased, and experimentation has been documented on Internet web fora. Although legal and illegal drugs are currently consumed with these e-devices, no scientific papers are available to support the observations reported by numerous media and web fora. Moreover, building on illegal drug vaping and vaporisation with e-devices (vaping misuse. Cannabis or cannabidiol (CBD) oils are often used in vape pens designed specifically for oils, they should not be used in standard e-liquids. There is a difference between vaping e-liquids and vaping oils, as they require different types of devices and have different safety considerations. Indeed, oil-based flavourings in typical e-cigarette device may cause lipid pneumonia when inhaled as hypothesized to be the main culprit of the EVALI outbreak (Gay et al. 2020).

In Table 6 a summary is given of the studies that analysed the chemical composition of DIY e-liquids. Several studies investigated the nicotine label discrepancy of DIY base ingredients and of DIY liquids from e-cigarette users. Base ingredients which were investigated are concentrated nicotine, propylene glycol bases and concentrated flavourings. Goniewicz et al. found that a pure nicotine e-liquid labelled to contain 210 mg/ml nicotine, actually contained 150 mg/ml nicotine (Goniewicz et al. 2015). This is less problematic than the findings of Davis et al., who found a substantial amount of nicotine in 'nicotine free' labelled concentrated flavours (two of the 30 nicotine-free samples contained concentrations of 14.2 mg/ml and 95.4 mg/ml) (Davis et al. 2016). Furthermore, some pure nicotine liquids have no labelled concentration and were found to contain up to more than 100 mg/ml nicotine (Davis et al. 2015).

The analysis of finished DIY products is not as straightforward as for commercial e-liquids because the nicotine concentration is not always declared for DIY e-liquids. Also the number of investigated samples is small compared to nicotine studies of commercial e-liquids. This is because of the difficulty to obtain DIY e-liquid samples. Cox et al. investigated 33 DIY e-liquid samples, of which 8 contained a nicotine concentration higher than 20% of the intented concentration and 2 lower as 20% (Cox et al. 2019). Barhdadi et al. investigated 3 DIY e-liquid samples of which 2 out of the 3 samples contained more than 20% of the intented concentration (Barhdadi et al. 2021)the e-cigarette has become a commonly used consumer product. In this study, we investigate whether regulatory changes had an impact on the quality of refill liquids (e-liquids. The risk of higher nicotine concentration in DIY e-liquid samples is not negligible as expected.

Besides the nicotine discrepancy, other chemical components were identified, such as flavourings and volatile organic compounds (VOCs). The majority of the identified flavouring chemicals have beenalso previously reported in commercial e-liquids. The investigated samples did not indicate a higher degree of variability in chemical profile compared to commercially available e-liquids (Cox et al. 2019; Berenguer, Pereira, et Camara 2021). Gschwend et al. found that flavouring-carrier fluid adducts, such as acetals, are characteristic of flavour concentrates due to the high concentration of flavour in a mixture with propylene glycol (Gschwend et al. 2023). They have identified a certain adduct that was exclusively found in DIY flavour concentrates: furfural PG acetal. In 58% of the analysed DIY flavouring concentrates they have identified at least one acetal adduct. The concern with these flavouring-acetal adducts is the limited toxicological information that is available. There are indication of certain toxicological concerns such as cytotoxicty to pulmonary epithelial cells and inhibition of the mitochondrial function in these type of cells (Jabba et al. 2020).

El Hellani et al. analyzed the emissions of DIY concentrates and e-liquids to which they added certain combinations of additives (El-Hellani et al. 2022). These additives include CBD, sucralose, ethyl maltol and an essential oil which wasn’t specified. ROS, carbonyls and phenol were assessed in the emissions. These generated similar toxicant exposure for commercial e-liquids, DIY concentrates and e-liquids with additives. In some cases, certain additives (CBD and sucralose) produced higher ROS emissions, while in other cases the same additives produced ROS emissions similar to unflavored PG/G e-liquid. It is therefore difficult to attribute the higher ROS emissions to a particular additive.

The current knowledge about the safety profiles of DIY e-liquids and their emissions is mainly similar to that of commercial e-liquids except for the case of unusual additives or combinations of ingredients. The question may also arise whether mixing of chemicals and additives might lead to an additional toxicity (Muthumalage et al. 2018)Mono Mac 6 (MM6. There is also less control over the dosage of DIY ingredients. While there are calculators, that may be used as aid for mixing ingredients, there is a risk of overdosing certain ingredients which could lead to a potential risk that is avoidable in commercial e-liquids. Farsalinos et al. tested concentrated flavours for the presence of diacetyl and acetyl propionyl and found that their concentration was three times higher than in commercial refill liquids (Farsalinos et al. 2015). Repeated exposure to these flavours in high doses may not be without risk.

Table 6: Summary of studies analysing the chemical composition of DIY e-liquids.

	Number samples	Nicotine discrepancy (>20%)	VOC's/ flavourings	Remarks
(Barhdadi et al. 2021)the e-cigarette has become a commonly used consumer product. In this study, we investigate whether regulatory changes had an impact on the quality of refill liquids (e-liquids	3	2 out of 3		
(Berenguer, Pereira, et Camara 2021)	2		characterization of the volatile components, mostly flavourings, in liquid and emission	e-liquids were prepared by vape shop vendor
(Cox et al. 2019)	33	30.3%	characterization of flavourings (acetoin, benzaldehyde, benzyl alcohol, maltol, 3-hexanol, piperonal)	e-liquids were obtained from e-cig users
(Davis et al. 2015)	3 (pure nicotine)	2 unknown declared concentration and 1 >20%		
(Davis et al. 2016)	30 (concentrated flavours)	4 (of which 2 <0.01mg/ml)		presence of 14.2 and 95.4 mg/ml nicotine (not labelled)
(El-Hellani et al. 2022)	27 (laboratory made)		addition of DIY additives yields similar toxicant exposure then refill liquids	
(Goniewicz et al. 2015)	1 (pure nicotine)	150 mg/ml instead of 210 mg/ml		
(Gschwend et al. 2023)			identification of acetal adducts in 58% of the analysed flavouring concentrates for DIY	
(Farsalinos et al. 2015)	46 (concentrated flavourings)		32 contained diacetyl and 10 samples contained acetyl propionyl both at concentration 3 times higher than refill liquids	

IV. Reactivity ageing

The shelf-life of e-liquids may be limited, constituents may deteriorate, or react with other constituents forming new substances. In the case where the e-liquid is in contact (e.g. cartridges or pods) with metal components of the e-cigarette device, transfer of metals from the device to the e-liquid may occur. Frequent use may also wear down critical parts of the e-cigarettes that are in contact with the e-liquid, such as the cartomizer (cartridge, tank and atomizer combined) which over time may increase the leachables into the e-liquid.

From the two search strategies used, seven articles were included that investigated the effect of storage on the composition of e-liquids. Findings about device properties that have already been covered in previous parts of the report are not repeated in this section.

Metals

Two studies were included that investigated the levels of metals in e-liquid during storage. Na et al., (2019) investigated metal content (Zn, Pb, Ni, Fe and Cr) in different commercial and a home-made e-liquid (PG/VG 1:1) after storage in the clearomizer (atomizer with a transparent tank) for up to seven days. It was found that general storage increased the content of Zn, Pb and Fe in the e-liquid. Mean concentration of Pb in e-liquids after seven days storage was approximately 2 mg/kg, which was an increase from approximately 0.1 mg/kg (approximately 0.1 mg/L). In the lab-made e-liquid, a similar trend in the metal content was not observed, indicating that the e-liquid formula may facilitate dissolution of metals from compartments in the e-cigarette that are in contact with the e-liquid. Indeed, in solutions consisting solely of propylene glycol and vegetable glycerine, the release rate of heavy metals was less apparent.

A similar study was performed by Jităreanu et al. (2022) showing an increase of the metals Pb, Ni and Zn in the e-liquid after storage for 5 days in two different clearomizers. Jitareanu and coworkers (2022) also showed that by increasing the storage temperature from 22°C to 40°C more metals leached into the e-liquid. The concentration of Pb in the e-liquid varied between approximately 1 mg/L to approximately 10 mg/L after 5 days of storage, depending on storage conditions and type of e-liquid.

All tested e-liquids contained less than 0.3 mg/L Pb before transfer to the clearomizer. Some differences were observed between the two different clearomizers regarding increases in the metal content of the e-liquids. One clearomizer appeared to release more Zn, whereas the other appeared to release more Pb. There were also some differences between the tested e-liquids indicating that the e-liquid composition may influence to what degree metals are dissolved from e-cigarette compartments. In general, a rise in temperature and storage time were associated with higher concentrations of heavy metals in the e-liquid.

Nicotine and nicotyrine

Nicotyrine, an alkaloid derived by the dehydrogenation of nicotine, has been described to inhibit nicotine metabolism (Abramovitz et al., 2015), which thereby may extend the clearance time of nicotine.

Two studies were included that investigated the levels of nicotyrine or nicotine in e-liquid during storage.

One of the included studies reported on the nicotyrine to nicotine ratio (NNR) in a purchased popular e-liquid as a function of time. The study investigated different storage conditions to reflect various real-life conditions, such as exposure to air, as well as light and temperature (Martinez et al., 2015).

According to the label on the purchased e-liquid, it contained nicotine (18mg/ml), PG, and VG and a “tobacco flavored” custom blend containing unspecified flavoring. The chemical composition of the e-liquid was analyzed at different time points over a period of approximately 65 days and under the various storage conditions. The e-liquid nicotyrine (and NNR) concentration increased throughout the time measured and for all storage-conditions tested. Storage conditions per se appeared to have little effect on the NNR.

Kosarac et al. (2023) reported on nicotine stability in various e-liquids containing either nicotine salt or free base nicotine. Those with nicotine salt had nicotine concentrations between 35–59 mg/mL, whereas free-base nicotine liquids had concentrations between 6–18 mg/mL. The samples were analyzed at six different time points over 24 weeks to simulate the stability of nicotine under accelerated storage conditions (40 °C and 75% relative humidity).

In all samples assayed, the amount of nicotine decreased from the initially measured amount over the period of 6 months except for two products with mint flavour. In most cases, a nicotine-10-oxide appeared to be the major degradation product, but its levels were not quantified. β-Nicotyrine, was also detected in 8 out of the 11 products studied.

Formation of e-liquid solvent adducts

Two studies were identified that investigated the formation of adducts between different additives, such as flavouring molecules to e-liquid solvents. The study by Erythropel and co-workers, investigated the formation of propylene glycol adducts caused by flavoring aldehydes in laboratory made e-liquids. They observed that acetal formation occurred during 14 days of storage at room temperature, with higher levels observed with increasing PG concentration of the e-liquid (Erythropel et al., 2019). The study by Gschwend and co-workers investigated the formation of adducts between a wider range of flavouring molecules (aldehydes, ketones, esters, alcohols, and others) with either methanol, PG or VG. The authors reported that of the 36 flavouring molecules investigated, 14 reacted with methanol and 12 reacted with PG or VG during four weeks of storage (Gschwend et al., 2023). Both studies showed formation of acetals in commercial e-liquids. The results of the two studies showed that flavouring molecules may react with the solvents of e-liquids during storage.

pH

One of the included study investigated the effect of storage on pH. pH was initially measured in 45 undiluted e-liquids, whereas only one e-liquid was tested after 4 months of storage at room temperature. The pH of the e-liquid investigated, was not affected by storage (Fairchild, 2021).

IV. Conclusion

In summary, presence of various harmful substances such as VOCs, PAHs and metals were reported in e-liquids for electronic cigarettes and heated tobacco products as well as in emissions from both product types.

Some of the substances identified were classified in one or more of the following hazard categories: carcinogenic, mutagenic, reprotoxic, endocrine disruptive, respiratory sensitizers or having organ specific toxicity upon repeated exposure.

It's important to note that various secondary harmful substances can be generated during the use of these products. This process may be affected by user behaviour, and the device design and material composition. For e-cigarettes, flavourings used in e-liquids may react with commonly used solvents, creating new substances. These new substances are also shown to be transferred to the e-cigarette aerosol and may be inhaled. These compounds may have toxicological effects different from their parental compounds, thus identification and quantification of such compounds in emissions are recommended for hazard- and risk assessment.

Metals may be released from different metal parts of the e-cigarette to the e-liquid upon contact. Parts of the device that may be in contact with the e-liquid include the coil, wires connecting the battery to the coil, and the soldering between the different metallic components. The quantities and type of metals that are released will depend on the composition of the alloy, the size of the contact area, the duration of contact and the e-liquid per se. Additives in the e-liquid that lower the pH may, for example, be a factor that may facilitate metal dissolution.

The composition of the aerosolized e-liquid that an user of e-cigarettes inhales will be affected by the type of device, the composition of the e-liquid, device settings (watt, volt, temperature), user pattern (puff duration, puff frequency) and coil aging. The influence of these variables on the emission is still largely unknown and therefore it is not possible to predict what a user is inhaling, based on information on the product and its use only. However, increasing the wattage, voltage or temperature may increase the e-liquid consumed and vaporized which thereby may increase the users exposure to hazardous substances. If the e-cigarette is used with a too high watt setting, the temperature of the coil may increase to such an extent that the levels of potentially harmful substances in the aerosol may increase above the emission levels expected when the device is used with the recommended settings. It also appears that malfunctioning e-cigarettes and dry puffing may increase the formation of potentially harmful substances, such as formaldehyde and acrolein. To minimize the levels of harmful aerosol constituents, the e-cigarette must be used within the settings recommended for the device and the coils.

The growing appeal of Do-It-Yourself (DIY) products is closely related to the attractiveness of characterizing flavours, as e-cigarette users can create their own blends. This practice, as well as the possibility of use of any type of substances not intended for e-cigarette use may increase the complexity and health hazard of the resulting aerosol. The DIY practice can also lead to improper ingredient handling raising the concern of accidental exposure to high concentrations of nicotine.

Based on these findings, European policy makers may consider the following regulatory recommendations:

1. Enhanced Enforcement of Ingredients Bans:

- Strengthen the enforcement mechanisms of existing bans on certain substances, such as those listed in the Tobacco Products Directive (TPD) under Article 7 and 20. Ensure that manufacturers adhere to these bans.
- Apply the precautionary principle to substances that are potentially harmful. Establish a mechanism for continuous monitoring and assessment of emerging scientific evidence on adverse effects of substances, allowing for immediate regulatory action if new information suggests potential harm.

2. Emission Bans or Mandated Reductions:

- Establish a comprehensive regulatory framework for e-cigarettes and heated tobacco products that addresses the evolving composition of these products. This should cover not only the substances present in the final product but also consider potential changes in composition before, during, and after use.
- Explore the implementation of emission bans or mandated reductions in harmful substances released during the use of e-cigarettes and heated tobacco products. Based on WHO recommendations[5], establish specific emission standards for key substances linked to health risks.

3. Extension of Regulation to Nicotine-Free Products:

- Amend existing regulations, such as the Tobacco Products Directive, to include and regulate nicotine-free e-cigarettes. Recognize that harmful substances may be present in products without nicotine and in their emissions.
- Apply consistent regulatory measures to both nicotine-containing and nicotine-free products to ensure the protection of public health.

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[5] Mandated lowering of toxicants in cigarette smoke: a description of the World Health Organization TobReg proposal - PMC (nih.gov)

4. Health Literacy and User Education:

- Develop and enhance health literacy among users of e-cigarettes. This should emphasize the potential health risks associated with different user behaviours, such as variations in product use and consumption patterns.

These policy recommendations aim to address the enforcement of existing bans, proactively manage potential risks, and continually improve the regulatory framework by considering new ingredient bans and emission standards. The integration of the precautionary principle ensures a forward-looking approach to safeguarding public health. Regular updates and adjustments to regulations, coupled with educational initiatives, can contribute to a safer and more informed use of these products.

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Appendix I

Device properties: Risk of bias evaluation

	Key questions									
Quality Criteria	1. Can we be confident in the exposure characterization?	2. Were experimental conditions identical across study groups?	3. Can we be confident in the outcome assessment?	4. Did the study have an adequate number of replicates per study group?	5. Did the study employ appropriate statistical approaches?	6. Were the properties (property) investigated, such as - watt, ohm or volts of the e-cigarette or different brands, components, adequately randomized/ weighted randomization?	7.Was allocation to study groups adequately concealed?	8.Were the research personnel blinded to the study group during the study?	9. Were outcome data complete without attrition or exclusion from analysis	10.Were all measured outcomes reported?
Definitely low ROB (++)	Direct evidence that the e-liquid used was independently characterized appropriate for the outcome assessed,, and if mixed in the laboratory, the purity of chemicals used were confirmed generally as ≥98%, AND direct evidence that the e-cigarette setting used, such as watt, volt or ohm were confirmed as the setting indicated.	Direct evidence that all conditions, except the property under investigation, were identical for all groups, AND the same e-liquid and puffing profile was used for control and experiment AND appropriate adjustments were made if appropriate for the outcome such as subtraction of blank values and use of positive control (such as a spiked sample) and negative control.	Direct evidence that the outcome was assessed using well-established methods (the gold standard). Reporting of LOD and LOQ for the outcome, and trapping efficacy, AND outcome assessed after the same length of time (number of puffs, puffing profile) in all study groups, AND there is direct evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes.	Outcome measurements for each study group were assessed using at least independent triplicates to address variability in response. (Three independent measurements from same e-cigarette was deemed to satisfy this requirement)	There is direct evidence that the study employed appropriate statistical methods	Direct evidence that the properties (property) under investigation were allocated including controls (comparison group(s)) using a method with a random component, AND direct evidence that the study used a concurrent control group as an indication that randomization covered all properties investigated.	Direct evidence that at the time of assigning the sequence of the different properties (property) investigated, such as watt, ohm or volts of the e-cigarette or different brands, components the research personnel did not know the allocation sequence, and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable	Direct evidence that the research personnel were adequately blinded, and it is unlikely that they could have broken the blinding during the study. Methods used to ensure blinding include central allocation, sequentially numbered treatment containers of identical appearance; or equivalent, OR the use of robotic testing systems during the study that are deemed to eliminate the opportunity for performance bias to influence results	Direct evidence that loss of experimental data was adequately addressed, and reasons were documented when data were removed from a study. Note: Acceptable handling of attrition includes: very little missing outcome data; reasons for missing data unlikely to be related to outcome (or for viability data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across study groups, with similar reasons for missing data across groups; missing outcomes is not enough to impact the effect.	Direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, AND In methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported. This would include outcomes reported with sufficient detail to be included in meta-analysis or fully tabulated during data extraction and analyses had been planned in advance.

	Key questions									
Probably low ROB (+)	Indirect evidence that the e-liquid used was independently characterized appropriate for the outcome assessed, and if mixed in the laboratory, the purity of chemicals used were confirmed generally as ≥98%, (i.e., the supplier of the chemical provides documentation of the purity of the chemical), AND indirect evidence that the e-cigarette setting used, such as watt, or volt were confirmed as the setting indicated (such as temperature of filament measured).	Assumed/ indirect evidence that all conditions, except the property under investigation, were identical for all groups, AND the same e-liquid and puffing profile was used for control and experiment AND appropriate adjustments were made if appropriate for the outcome such as subtraction of blank values and use of positive control (such as a spiked sample) and negative control.	Indirect evidence that the outcome was assessed using acceptable methods (i.e., deemed valid and reliable but not the gold standard), AND outcome assessed after the same length of time (number of puffs, puffing profile) in all study groups, OR it is deemed that the outcome assessment methods used would not appreciably bias results, AND there is indirect evidence that the outcome assessors were adequately blinded to the study group, and it is unlikely that they could have broken the blinding prior to reporting outcomes, OR it is deemed that lack of adequate blinding of outcome assessors would not appreciably bias results, which is more likely to apply to objective outcome measures.	Outcome measurements for each study group were assessed in duplicate to address variability in response.	There is indirect evidence that the study employed appropriate statistical methods	Indirect evidence that the properties (property) under investigation were allocated including controls (comparison group(s)) using a method with a random component (i.e., authors state random allocation, without description of the method), AND evidence that the study used a concurrent control group as an indication that randomization covered all properties investigated. OR it is deemed that allocation without a clearly random component would not appreciably bias results.	Indirect evidence that at the time of assigning study groups the research personnel did not know what the sequence of the different properties (property) under investigation and it is unlikely that they could have broken the blinding of allocation until after assignment was complete and irrevocable, OR it is deemed that lack of adequate allocation concealment would not appreciably bias results.	Indirect evidence that the research personnel were adequately blinded to study group, and it is unlikely that they could have broken the blinding during the study, OR it is deemed that lack of adequate blinding during the study would not appreciably bias results.	Indirect evidence that loss of data was adequately addressed, and reasons were documented when data was removed from a study, OR it is deemed that the proportion lost would not appreciably bias results.	Indirect evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have been reported, OR analyses that had not been planned in advance (i.e., retrospective unplanned subgroup analyses) are clearly indicated as such and deemed that unplanned analyses were appropriate and selective reporting would not appreciably bias results (e.g., appropriate analyses of an unexpected effect). This would include outcomes reported with insufficient detail such as only reporting that results were statistically significant (or not).

	Key questions									
Probably high ROB (-)	Indirect evidence that the e-liquid used was assessed using poorly validated methods AND indirect evidence that the e-cigarette setting used, such as watt, volt or ohm were assessed using poorly validated methods. OR there is insufficient information provided about the validity of the assessment method, but no direct evidence for concern (record “NR” as basis for answer). OR not reported, but not of high concern.	Indirect evidence that not all conditions, except the property under investigation, were identical for all groups.	Indirect evidence that the outcome assessment method is an insensitive method/ instrument, OR the length of time (number of puffs, puffing profile) differed by study group, OR there is indirect evidence that it was possible for outcome assessors to infer the study group prior to reporting outcomes without sufficient quality control measures, OR there is insufficient information provided about blinding of outcome assessors (record “NR” as basis for answer).	The number of replicates for outcome measurements was not reported.	There is indirect evidence that the study did not use appropriate statistical methods or consistency between statistical method used and reporting not appropriate.	Indirect evidence the properties (property) under investigation were allocated using a method with a non-random component, OR indirect evidence that there was a lack of a concurrent control group, OR there is insufficient information provided about how the properties (property) under investigation was allocated (record “NR” as basis for answer).	Indirect evidence that at the time of assigning study groups it was possible for the research personnel to know the sequence of the different properties (property) under investigation, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable, OR there is insufficient information provided about allocation to study groups (record “NR” as basis for answer).	Indirect evidence that the research personnel were not adequately blinded to study group, OR there is insufficient information provided about blinding to study group during the study (record “NR” as basis for answer).	Indirect evidence that loss of data was unacceptably large and not adequately addressed, OR there is insufficient information provided about loss of data (record “NR” as basis for answer).	Indirect evidence that all of the study’s measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported, OR and there is indirect evidence that unplanned analyses were included that may appreciably bias results, OR there is insufficient information provided about selective outcome reporting (record “NR” as basis for answer).

	Key questions									
Definitely high ROB (--)	Direct evidence that the e-liquid used was assessed using poorly validated methods and, direct evidence that the e-cigarette setting used, such as watt, volt or ohm were assessed using poorly validated methods. OR not reported, and of high concern.	Direct evidence that not all conditions, except the property under investigation, were identical for all groups.	Direct evidence that the outcome assessment method is an insensitive method/ instrument, or there is missing essential information to interpret the outcome. OR the length of time (number of puffs, puffing profile) differed by study group, OR there is direct evidence for lack of adequate blinding of outcome assessors, including no blinding or incomplete blinding without quality control measures.	Outcome measurements for each study group were not assessed more than once.	There is direct evidence that the study did not use appropriate statistical methods or did not use any statistical methods to compare control and treated groups. OR statistical method not reported.	Direct evidence that the properties (property) under investigation were allocated using a method with a non-random component including judgment of the investigator or the results of laboratory tests, OR direct evidence that there was a lack of a concurrent control group (comparison group).	Direct evidence that at the time of assigning study groups it was possible for the research personnel to know the sequence of the different properties (property) under investigation, or it is likely that they could have broken the blinding of allocation before assignment was complete and irrevocable.	Direct evidence that the research personnel were not adequately blinded to study group.	Direct evidence that loss of data was unacceptably large and not adequately addressed. Note: Unacceptable handling of attrition or exclusion includes: reason for loss is likely to be related to true outcome, with either imbalance in numbers or reasons for loss across study groups.	Direct evidence that all of the study's measured outcomes (primary and secondary) outlined in the protocol, methods, abstract, and/or introduction (that are relevant for the evaluation) have not been reported. In addition to not reporting outcomes, this would include reporting outcomes based on composite score without individual outcome components or outcomes reported using measurements, analysis methods or subsets of the data (e.g., subscales) that were not pre-specified or reporting outcomes not pre-specified, or that unplanned analyses were included that would appreciably bias results.

The Risk of bias evaluation is based on the OHAT protocol for in vitro studies (1), and *two criteria were retrieved from the systematic review by Prueitt and co-workers (2). Overall evaluation of ROB is based on The Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration (3).

1: Rooney et al., (2015). (OHAT) https://ntp.niehs.nih.gov/sites/default/files/ntp/ohat/pfoa_pfos/protocol_201506_508.pdf

2: Prueitt et al., (2020). Systematic review of the potential respiratory carcinogenicity of metallic nickel in humans, Crit Rev Toxicol. 2020 Aug;50(7):605-639.doi: 10.1080/10408444.2020.1803792.

3: Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Toxicology Program Office of Health Assessment and Translation (OHAT, 2019)

Appendix II : Search strings

Device properties

Update of search: Adverse health effects of electronic cigarette use: an umbrella review and toxicological evaluation

Contact person:	Håkon Valen/Rune Becher
earch:	Trude Anine Muggerud
Reviewer:	Marita Heintz
Commentary:	Update of search in November 2021

<table>
<tr><th colspan="4">What questions should the literature search answer?</th></tr>
<tr><td colspan="4">Everything that is found regarding e-cigarettes</td></tr>
<tr><th colspan="4">Question in PICO-form</th></tr>
<tr><th>Population</th><th>Intervention</th><th>Comparison</th><th>Outcome</th></tr>
<tr><td></td><td>E-cigarettes
Nicotine waterpipe
Nicotine vapor</td><td></td><td>Health risk
[not searched]</td></tr>
</table>

Database: Web of Science

Date: 31.03.2023

Number of references: 93 systematic reviews, 1928 other references.

#5	#2 NOT #4	1,928
#4	#2 AND #3	93
#3	TS=((”systematic*” NEAR/1 ”review*”) or (”review” and ((”structured” or ”database*” or ”systematic*”) NEAR/1 ”search*”)) or ”integrative review*” or (”evidence” NEAR/1 ”review*”)) OR TI=(”metaanal*” or ”meta anal*”) OR AB=(”metaanal*” or ”meta anal*”)	546,347
#2	TS=(((“electronic cigarette$” or “e-cigarette$” or “ecigarette$” or “eCIG*” or “e-CIG*” or “electronic nicotine delivery system$” or “electronic nicotine delivery device$” or “nicotin* vapor*” or “nicotin* vapour*” or “vaporised nicotin*” or “vaporized nicotin*” or “vapourised nicotin*” or “vapourized nicotin*” or “e-hookah$” or “Electronic Hookah$” or “Hookah Pen$”))) Limit to: Timespan 2021-11-23 – 2023-03-30	2,020
#1	TS=(((“electronic cigarette$” or ”e-cigarette$” or ”ecigarette$” or ”eCIG*” or ”e-CIG*” or ”electronic nicotine delivery system$” or ”electronic nicotine delivery device$” or ”nicotin* vapor*” or ”nicotin* vapour*” or ”vaporised nicotin*” or ”vaporized nicotin*” or ”vapourised nicotin*” or ”vapourized nicotin*” or ”e-hookah$” or ”Electronic Hookah$” or ”Hookah Pen$”)))	11,610

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions <1946 to March 29, 2023>

Date: 31.03.2023

Number of references: 158 systematic reviews, 2876 other references

1	Electronic Nicotine Delivery Systems/ or (”Electronic Cigarette?” or ”E-Cigarette?” or ”E Cigarette?” or ”E-Cig?” or ”E Cig?” or ”ecigarette$” or ”eCIG*” or ”Electronic Nicotine Delivery System?” or ”Electronic Nicotine Delivery Device?”).tw,kf.	10763
2	(”nicotin* vapor*” or ”nicotin* vapour*” or ”vapori#ed nicotin*” or ”vapouri#ed nicotin*”).tw,kf.	125
3	(”e-hookah?” or ”e hookah?” or ”Electronic Hookah?” or ”Hookah Pen?”).tw,kf.	31
4	Vaping/ or (Vape? or vaping).tw,kf.	5068
5	or/1-4	11534
6	(2022* or 2023*).ed,ep,yr,dp,dt.	2123837
7	(202111* or 202112*).ep,ed,dt.	491607
8	or/6-7	2496568
9	5 and 8	3034
10	limit 9 to ”reviews (maximizes specificity)”	127
11	Meta-Analysis/ or Network Meta-Analysis/ or ((systematic* adj2 review*) or metaanal* or ”meta anal*” or (review and ((structured or database* or systematic*) adj2 search*)) or ”integrative review*” or (evidence adj2 review*)).tw,kf,bt.	495729
12	10 or (9 and 11)	158
13	9 not 12	2876

Database: Embase <1974 to 2023 March 29>

Date: 31.03.23

Number of references: 126 systematic reviews, 2163 other references

1	electronic cigarette/ or (”Electronic Cigarette?” or ”E-Cigarette?” or ”E Cigarette?” or ”E-Cig?” or ”E Cig?” or ”ecigarette$” or ”eCIG*” or ”Electronic Nicotine Delivery System?” or ”Electronic Nicotine Delivery Device?”).tw,kf.	14100
2	(”nicotin* vapor*” or ”nicotin* vapour*” or ”vapori#ed nicotin*” or ”vapouri#ed nicotin*”).tw,kf.	193
3	(”e-hookah?” or ”e hookah?” or ”Electronic Hookah?” or ”Hookah Pen?”).tw,kf.	46
4	vaping/ or (Vape? or vaping).tw,kf.	6700
5	or/1-4	15529
6	conference abstract.pt.	4712052
7	5 not 6	13307
8	limit 7 to embase	8802
9	(2022* or 2023*).yr,dd,dp,dc.	3012945
10	(202111* or 202112*).dd,dc.	312142
11	9 or 10	3304337
12	8 and 11	2289
13	limit 12 to ”reviews (maximizes specificity)”	73
14	exp Meta-Analysis/ or ”systematic review”/ or ((systematic* adj2 review*) or metaanal* or ”meta anal*” or (review and ((structured or database* or systematic*) adj2 search*)) or ”integrative review*” or (evidence adj2 review*)).tw,kf,bt.	744745
15	13 or (12 and 14)	126
16	12 not 15	2163

Database: Cochrane Database of Systematic Reviews Issue 3 of 12, March 2023

Date: 31.03.2023

Commentary: For Cochrane-references, limit by date via Cochrane Library publication date. For trials, it is necessary to both limit on date via Cochrane Library publication date and Central Trials only original publication year. This must be done in two sequences.

Number of references: 3 systematic reviews. 368 other references.

#1	[mh ^”Electronic Nicotine Delivery Systems”]	335
#2	((Electronic NEXT Cigarette?) or (E NEXT Cigarette?) or (E NEXT Cig?) or ecigarette? or eCIG* or (”Electronic Nicotine Delivery” NEXT System?) or (”Electronic Nicotine Delivery” NEXT Device?)):ti,ab	981
#3	((nicotin* NEXT vapor*) or (nicotin* NEXT vapour*) or (vapori?ed NEXT nicotin*) or (vapouri?ed NEXT nicotin*)):ti,ab	29
#4	((e NEXT hookah?) or (Electronic NEXT Hookah?) or (Hookah NEXT Pen?)):ti,ab	6
#5	[mh ^”Vaping”]	130
#6	(Vape? or vaping):ti,ab	295
#7	{OR #1-#6}	1129
#8	{OR #1-#6} with Cochrane Library publication date Between Nov 2021 and Mar 2023, in Cochrane Reviews	3
#9	{OR #1-#6} with Publication Year from 2021 to 2023, in Trials	354
#10	{OR #1-#6} with Cochrane Library publication date Between Nov 2021 and Mar 2023, in Trials	259
#11	#9 or #10	368

DIY practice

(”DIY”[All Fields] OR ”do-it-yourself”[All Fields] OR ”homemade”[All Fields] OR ”concentrated”[All Fields] OR ”modifications”[ALL Fields] OR ”customization*” OR ”e-juice mixing”) AND (”electronic nicotine delivery systems”[MeSH Terms] OR ”ecigarette*”[Title/Abstract] OR ”electronic cigarette”[Title/Abstract] OR ”e-cig”[Title/Abstract] OR ”ecig”[Title/Abstract] OR ”e liquid*”[Title/Abstract]).

Reactivity/Ageing

Pubmed

(((“shelf life”[Title/Abstract]) OR (“ageing”[Title/Abstract])) OR ((aging[Title/Abstract] OR expiry date[Title/Abstract] OR storage[Title/Abstract] OR stored[Title/Abstract] OR “storing condition*”[Title/Abstract] OR shelf-life[Title/Abstract]))) AND ((((“electronic nicotine delivery systems”[MeSH Terms]) OR ecigarette*[Title/Abstract] OR electronic cigarette*[Title/Abstract] OR electronic cigs[Title/Abstract] OR e-cig*[Title/Abstract] OR ecig*[Title/Abstract] OR e-liquid*[Title/Abstract])) AND (degradation products[Title/Abstract] OR “effects of ph”[Title/Abstract] OR material instabilities[Title/Abstract] OR metal analysis[Title/Abstract] OR metal concentrations[Title/Abstract] OR stability testing[Title/Abstract] OR stability*[Title/Abstract]))

Embase

(((‘shelflife’:ti,ab) OR (ageing:ti,ab)) OR ((aging:ti,ab OR ‘expirydate’:ti,ab OR storage:ti,ab OR stored:ti,ab OR ‘storingcondition*’:ti,ab OR shelflife:ti,ab))) AND ((((‘electronicnicotinedeliverysystems’/exp) OR ecigarette*:ti,ab OR ‘electroniccigarette*’:ti,ab OR ‘electroniccigs’:ti,ab OR e-cig*:ti,ab OR ecig*:ti,ab OR e-liquid*:ti,ab)) AND (‘degradationproducts’:ti,ab OR ‘effectsofph’:ti,ab OR ‘materialinstabilities’:ti,ab OR ‘metal analysis’:ti,ab OR ‹metal concentrations›:ti,ab OR ‹stability testing›:ti,ab OR stability*:ti,ab))

Scopus

(((TITLE-ABS (“shelf life”)) OR (TITLE-ABS (ageing))) OR ((TITLE-ABS (aging) OR TITLE-ABS (“expiry date”) OR TITLE-ABS (storage) OR TITLE-ABS (stored) OR TITLE-ABS (“storing condition*”) OR TITLE-ABS (shelf-life)))) AND ((((INDEXTERMS (“electronic nicotine delivery systems”)) OR TITLE-ABS (ecigarette*) OR TITLE-ABS (“electronic cigarette*”) OR TITLE-ABS (“electronic cigs”) OR TITLE-ABS (e-cig*) OR TITLE-ABS (ecig*) OR TITLE-ABS (e-liquid*))) AND (TITLE-ABS (“degradation products”) OR TITLE-ABS (“effects of ph”) OR TITLE-ABS (“material instabilities”) OR TITLE-ABS (“metal analysis”) OR TITLE-ABS (“metal concentrations”) OR TITLE-ABS (“stability testing”) OR TITLE-ABS (stability*)))

EPPI-Reviewer 6

Keywords used for search in EPPI-Reviewer 6: Headspace, aged, aging, shelf, shelf life, storage.

Appendix III

CAS Number	Substance	Carcino-genicity					Mutagen-icity	Reprotoxicity	Endo-crine disruptor					Other effects							
						ECHA (CLP)															
		ECHA (CLP)	IARC	US EPA		ACGIH	ECHA (CLP)	ECHA (CLP)	BKH-DHI		SIN LIST	US EPA	TEDX	Resp. Sens	Skin Sens.	Skin Irrit.	Eye Irrit.	Acute Tox.	Asp. Tox.	STOT SE	STOT RE
		H.		C.	Y.	C.	H.	H.	C.	Y.				H.	H.	H.	H.	H.	H.	H.	H.
57653-85-7	1,2,3,6,7,8-hexa CDD	NA	NA	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
40321-76-4	1,2,3,7,8-penta CDD	NA	NA	NA		NA	NA	NA	C.1	EM 1999	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
57117-41-6	1,2,3,7,8-penta CDF	NA	NA	NA		NA	NA	NA	C.2	EM 1999	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
107-06-2	1,2-dichloroethane	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A4	NA	NA	NA		YES	List 2	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	STOT SE 3	NA
78-87-5	1,2-dichloropropane	1B	1	NA		A4	NA	NA	NA		YES	List 2	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
106-99-0	1,3-butadiene	1A	1	Carcinogenic to humans		A2	1B	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
106-46-7	1,4-dichlorobenzene	2	2B	NA		A3	NA	NA	NA		NA	List 2	NA	NA	NA	NA	Eye Irrit. 2	NA	NA	NA	NA
26148-68-5	1-amino-3-methyl-9H-pyrido-[2,3,b]indole (MeAaC)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
930-55-2	1-Nitrosopyrrolidine (NPYR)	NA	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
57117-31-4	2,3,4,7,8-penta CDF	NA	1	NA		NA	NA	NA	C.1	EM 1999	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
1746-01-6	2,3,7,8-tetra CDD	NA	1	NA		NA	NA	NA	C.1	EM 1999	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
51207-31-9	2,3,7,8-tetra CDF	NA	NA	NA		NA	NA	NA	C.2	EM 1999	NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
87-62-7	2,6-dimethylaniline	2	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	STOT SE 3	NA

105650-23-5	2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
67730-11-4	2-amino-6-methyldipyrido[1,2-a:3’,2’-d]imidazole (Glu-P-1)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
67730-10-3	2-aminodipyrido[1,2-a:3’,2’-d]imidazole (Glu-P-2)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
91-59-8	2-aminonaphthalene	1A	1	NA		A1	NA	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
79-46-9	2-nitropropane	1B	2B	NA		A3	NA	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
62450-06-0	3-amino-1,4-dimethyl-5H-pyrido(4,3-b)indole (Trp-P-1)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
62450-07-1	3-Amino-1-methyl-5H-pyrido[4,3-b]indole (Trp-P-2)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
96-24-2	3-chloro-1,2-propandiol	NA	2B	NA		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
92-67-1	4-aminobiphenyl	1A	1	NA		A1	NA	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
108-10-1	4-methyl-2-pentanone	2	2B	Data are inadequate for an assessment of human carcinogenic potential		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	STOT SE 3	NA
3697-24-3	5-methylchrysene	NA	2B	NA		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
75-07-0	Acetaldehyde	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	2	NA	NA		NA	List 2	YES	NA	NA	NA	Eye Irrit. 2	NA	NA	STOT SE 3	NA
60-35-5	Acetamide	2	2B	NA		NA	NA	NA	NA		NA	List 2	NA	NA	NA	NA	NA	NA	NA	NA	NA
107-02-8	Acrolein	NA	2A	Data are inadequate for an assessment of human carcinogenic potential		A4	NA	NA	NA		NA	List 2	NA	NA	NA	Skin Corr. 1B	NA	Acute Tox. 1	NA	NA	NA
79-06-1	Acrylamide	1B	2A	Likely to be carcinogenic to humans		A3	1B	2	NA		YES	List 2	NA	NA	Skin Sens. 1	NA	Eye Irrit. 2	Acute Tox. 3	NA	NA	STOT RE 1
107-13-1	Acrylonitrile	1B	2B	B1 (Probable human carcinogen - based on limited evidence of carcinogenicity in humans)		A3	NA	NA	NA		YES	NA	YES	NA	Skin Sens. 1	NA	Eye Dam. 1	Acute Tox. 3	NA	STOT SE 3	NA
71-43-2	Benzene	1A	1	Known/likely human carcinogen		A1	1B	NA	NA		YES	List 2	YES	NA	NA	NA	Eye Irrit. 2	NA	Asp. Tox. 1	NA	STOT RE 1

92-87-5	Benzidine	1A	1	A (Human carcinogen)		A1	NA	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
56-55-3	Benzo(a)anthracene	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A2	NA	NA	C.2	BKH 2002	YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
50-32-8	Benzo(a)pyrene	1B	1	Carcinogenic to humans		A2	1B	1B	C.1	BKH 2002	YES	List 2	YES	NA	Skin Sens. 1	NA	NA	NA	NA	NA	NA
205-99-2	Benzo(b)fluoranthene	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A2	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
271-89-6	Benzo(b)furan	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
195-19-7	Benzo(c)phenanthrene	NA	2B	NA		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
192-97-2	Benzo(e)pyrene	1B	3	NA		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
202-33-5	Benzo(j)aceanthrylene	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
207-08-9	Benzo(k)fluoranthene	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
75-27-4	Bromodichloromethane	NA	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
331-39-5	Caffeic acid	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
630-08-0	Carbon monoxide	NA	NA	NA		NA	NA	1A	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 3	NA	NA	STOT RE 1
120-80-9	Catechol	1B	2B	NA		A3	2	NA	NA		NA	NA	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	NA	NA
67-66-3	Chloroform	2	2B	Not likely to be carcinogenic to humans		A3	NA	2	NA		NA	NA	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	NA	STOT RE 1
218-01-9	Chrysene	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	2	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
123-73-9	Crotonaldehyde	NA	NA	C (Possible human carcinogen)		NA	2	NA	NA		NA	NA	YES	NA	NA	NA	Eye Dam. 1	Acute Tox. 2	NA	STOT SE 3	STOT RE 2
27208-37-3	Cyclopenta(c,d)pyrene	NA	2A	NA		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA

53-70-3	Dibenz(a,h)anthracene	1B	2A	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
189-64-0	Dibenz(a,h)pyrene	1B	2B	NA		NA	2	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
189-55-9	Dibenz(a,i)pyrene	1B	2B	NA		NA	2	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
191-30-0	Dibenz(a,l)pyrene	1B	2A	NA		NA	2	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
64-17-5	Ethanol	NA	1	NA		A3	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
100-41-4	Ethylbenzene	NA	2B	D (Not classifiable as to human carcinogenicity)		A3	NA	NA	NA		NA	List 2	YES	NA	NA	NA	NA	Acute Tox. 4	Asp. Tox. 1	NA	STOT RE 2
75-21-8	Ethylene oxide	1B	1	Carcinogenic to humans		A2	1B	1B	NA		YES	NA	YES	NA	NA	Skin Corr. 1	Eye Dam. 1	Acute Tox. 3	NA	STOT SE 3	STOT RE 1
50-00-0	Formaldehyde	1B	1	B1 (Probable human carcinogen - based on limited evidence of carcinogenicity in humans)		A2	2	NA	NA		YES	NA	YES	NA	Skin Sens. 1	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	NA
110-00-9	Furan	1B	2B	NA		NA	2	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	STOT RE 2
556-52-5	Glycidol	1B	2A	NA		A3	2	1B	NA		YES	NA	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	STOT SE 3	NA
107-22-2	Glyoxal	NA	NA	NA		A4	2	NA	NA		NA	NA	NA	NA	Skin Sens. 1	NA	Eye Irrit. 2	Acute Tox. 4	NA	NA	NA
302-01-2	Hydrazine	1B	2A	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	NA	NA	NA		YES	List 2	NA	NA	Skin Sens. 1	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	NA
123-31-9	Hydroquinone	2	3	NA		A3	2	NA	NA		NA	NA	YES	NA	Skin Sens. 1	NA	Eye Dam. 1	Acute Tox. 4	NA	NA	NA
193-39-5	Indeno(1,2,3-cd)pyrene	NA	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
78-79-5	Isoprene	1B	2B	NA		NA	2	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
108-39-4	m-cresol	NA	NA	C (Possible human carcinogen)		NA	NA	NA	NA		NA	NA	NA	NA	NA	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	NA
1634-04-4	Methyl tert-butyl ether	NA	3	NA		A3	NA	NA	C.1	DHI 2006	YES	List 2	YES	NA	NA	NA	NA	NA	NA	NA	NA

75-09-2	Methylene chloride	2	2A	Likely to be carcinogenic to humans		A3	NA	NA	NA		NA	List 2	YES	NA	NA	NA	NA	NA	NA	NA	NA
91-20-3	Naphthalene	2	2B	C (Possible human carcinogen)		A4	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
110-54-3	n-hexane	NA	NA	Inadequate information to assess carcinogenic potential		NA	NA	2	NA		YES	List 2	YES	NA	NA	NA	NA	NA	Asp. Tox. 1	STOT SE 3	STOT RE 2
98-95-3	Nitrobenzene	2	2B	Likely to be carcinogenic to humans		A3	NA	1B	NA		YES	List 2	YES	NA	NA	NA	NA	Acute Tox. 3	NA	NA	STOT RE 1
75-52-5	Nitromethane	NA	2B	NA		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
924-16-3	N-Nitrosodibutylamine (NDBA)	NA	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1116-54-7	N-Nitrosodiethanolamine (NDELA)	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		YES	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
55-18-5	N-Nitrosodiethylamine (NDEA)	NA	2A	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
62-75-9	N-Nitrosodimethylamine (NDMA)	1B	2A	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	NA	NA	NA		YES	List 2	NA	NA	NA	NA	NA	Acute Tox. 2	NA	NA	STOT RE 1
59-89-2	N-nitrosomorpholine (NMOR)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
100-75-4	N-nitrosopiperidine (NPIP)	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
90-04-0	o-anisidine	1B	2A	NA		A3	2	NA	NA		YES	NA	NA	NA	NA	NA	NA	Acute Tox. 3	NA	NA	NA
95-48-7	o-cresol	NA	NA	C (Possible human carcinogen)		NA	NA	NA	NA		NA	NA	NA	NA	NA	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	NA
95-53-4	o-toluidine	1B	1	NA		A3	NA	NA	NA		YES	List 2	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	NA	NA
106-44-5	p-Cresol	NA	NA	C (Possible human carcinogen)		NA	NA	NA	C.2	DHI 2006	NA	NA	NA	NA	NA	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	NA
108-95-2	Phenol	NA	3	D (Not classifiable as to human carcinogenicity)		A4	2	NA	NA		NA	NA	YES	NA	NA	Skin Corr. 1B	NA	Acute Tox. 3	NA	NA	STOT RE 2

75-56-9	Propylene Oxide	1B	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	1B	NA	NA		YES	NA	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	STOT SE 3	NA
110-86-1	Pyridine	NA	2B	NA		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
91-22-5	Quinoline	1B	2B	Known/likely human carcinogen		NA	2	NA	NA		YES	List 2	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	NA	NA
108-46-3	Resorcinol	NA	3	NA		A4	NA	NA	C.1	EM 1999	YES	NA	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	NA	NA
100-42-5	Styrene	NA	2A	NA		A4	NA	2	C.1	EM 1999	YES	List 2	YES	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	NA	STOT RE 1
127-18-4	Tetrachloroethylene	2	2A	Likely to be carcinogenic to humans		A3	NA	NA	C.2	EM 1999	YES	List 2	YES	NA	NA	NA	NA	NA	NA	NA	NA
108-88-3	Toluene	NA	3	Inadequate information to assess carcinogenic potential		A4	NA	2	NA		NA	List 1 (Waiting for SDWA test)	YES	NA	NA	NA	NA	NA	Asp. Tox. 1	STOT SE 3	STOT RE 2
79-01-6	Trichloroethylene	1B	1	Carcinogenic to humans		A2	2	NA	NA		YES	List 2	YES	NA	NA	NA	Eye Irrit. 2	NA	NA	STOT SE 3	NA
108-05-4	Vinyl Acetate	2	2B	NA		A3	NA	NA	C.3b	BKH 2002	NA	NA	YES	NA	NA	NA	NA	Acute Tox. 4	NA	STOT SE 3	NA
75-01-4	Vinyl Chloride	1A	1	Known/likely human carcinogen		A1	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
98-01-1	2-furaldehyde	2	3	NA		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	STOT SE 3	NA
98-00-0	2-furanmethanol	2	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 3	NA	STOT SE 3	STOT RE 2
591-78-6	2-Hexanone	NA	NA	Inadequate information to assess carcinogenic potential		NA	NA	2	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	STOT SE 3	STOT RE 1
67-64-1	Acetone	NA	NA	Data are inadequate for an assessment of human carcinogenic potential		A4	NA	NA	NA		NA	List 1 (Conclusion négative sur la présence d'un potentiel PE)	YES	NA	NA	NA	Eye Irrit. 2	NA	NA	STOT SE 3	NA
75-86-5	Acetone cyanohydrin	NA	NA	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 1	NA	NA	NA
120-12-7	Anthracene	NA	2B	D (Not classifiable as to human carcinogenicity)		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
75-15-0	Carbon disulfide	NA	NA	NA		A4	NA	2	C.2	EM 1999	YES	NA	YES	NA	NA	NA	Eye Irrit. 2	NA	NA	NA	STOT RE 1

75-00-3	Chloroethane	2	3	NA		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
74-87-3	Chloromethane	2	3	Carcinogenic potential cannot be determined		A4	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	STOT RE 2
96-33-3	Methylacrylate	NA	2B	D (Not classifiable as to human carcinogenicity)		A4	NA	NA	NA		NA	NA	YES	NA	Skin Sens. 1	NA	Eye Irrit. 2	Acute Tox. 4	NA	STOT SE 3	NA
85-01-8	Phenanthrene	NA	3	D (Not classifiable as to human carcinogenicity)		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
7440-38-2	Arsenic	NA	1	A (Human carcinogen)		A1	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	Acute Tox. 3	NA	NA	NA
7440-48-4	Cobalt	1B	2A	NA		A3	2	1B	NA		NA	NA	NA	Resp. Sens. 1	Skin Sens. 1	NA	NA	NA	NA	NA	NA
7439-92-1	Lead	NA	2B	B2 (Probable human carcinogen - based on sufficient evidence of carcinogenicity in animals)		A3	NA	1A	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
7439-97-6	Mercury	NA	3	D (Not classifiable as to human carcinogenicity)		A4	NA	1B	NA		YES	NA	YES	NA	NA	NA	NA	Acute Tox. 2	NA	NA	STOT RE 1
7782-49-2	Selenium	NA	3	D (Not classifiable as to human carcinogenicity)		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 3	NA	NA	STOT RE 2
7440-41-7	Beryllium	1B	1	B1 (Probable human carcinogen - based on limited evidence of carcinogenicity in humans)		A1	NA	NA	NA		YES	NA	NA	NA	Skin Sens. 1	NA	Eye Irrit. 2	Acute Tox. 2	NA	STOT SE 3	STOT RE 1
7440-43-9	Cadmium	1B	1	B1 (Probable human carcinogen - based on limited evidence of carcinogenicity in humans)		A2	2	2	NA		YES	NA	YES	NA	NA	NA	NA	Acute Tox. 2	NA	NA	STOT RE 1
7440-47-3	Chromium	NA	3	NA		A1	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
7440-02-0	Nickel	2	2B	NA		A5	NA	NA	NA		NA	NA	NA	NA	Skin Sens. 1	NA	NA	NA	NA	NA	STOT RE 1
65-85-0	BENZOIC ACID	NA	NA	D (Not classifiable as to human carcinogenicity)		NA	NA	NA	NA		NA	NA	YES	NA	NA	NA	Eye Dam. 1	NA	NA	NA	STOT RE 1
77-93-0	TRIETHYL CITRATE	1A	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
69-72-7	SALICYLIC ACID	NA	NA	NA		NA	NA	2	NA		NA	NA	NA	NA	NA	NA	Eye Dam. 1	Acute Tox. 4	NA	NA	NA
77-53-2	CEDROL	1B	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	Asp. Tox. 1	NA	NA

77-83-8	ETHYL METHYLPHENYLGLYCIDATE	1A	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
123-35-3	MYRCENE	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
119-36-8	METHYL SALICYLATE	NA	NA	NA		NA	NA	2	NA		NA	NA	YES	NA	Skin Sens. 1B	NA	NA	Acute Tox. 4	NA	NA	NA
89-82-7	PULEGONE	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
78-59-1	ISOPHORONE	2	2B	C (Possible human carcinogen)		A3	NA	NA	NA		NA	List 1 (Negative conclusion on ED potential)	NA	NA	NA	NA	Eye Irrit. 2	Acute Tox. 4	NA	STOT SE 3	NA
98-02-2	FURFURYL MERCAPTAN	NA	NA	NA		NA	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	Acute Tox. 1	NA	NA	NA
76-49-3	BORNYL ACETATE	1A	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
128-37-0	BUTYLATED HYDROXYTOLUENE	NA	3	NA		A4	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
548-62-9	METHYLROSANILINIUM CHLORIDE	2	2B	NA		NA	NA	NA	NA		YES	NA	NA	NA	NA	NA	Eye Dam. 1	Acute Tox. 4	NA	NA	NA
541-02-6	DECAMETHYLCYCLOPENTASILOXANE	NA	NA	NA		NA	NA	NA	NA		YES	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
97-99-4	TETRAHYDROFURFURYL ALCOHOL	NA	NA	NA		NA	NA	1B	NA		YES	NA	NA	NA	NA	NA	Eye Irrit. 2	NA	NA	NA	NA
97-88-1	N-BUTYL METHACRYLATE	NA	2B	NA		NA	NA	NA	NA		NA	NA	NA	NA	Skin Sens. 1	NA	Eye Irrit. 2	NA	NA	STOT SE 3	NA
1303-86-2	BORON OXIDE	NA	NA	NA		NA	NA	1B	NA		YES	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
1333-86-4	CARBON BLACK	NA	2B	NA		A3	NA	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
4170-30-3	CROTONALDEHYDE	NA	2B	NA		A3	2	NA	NA		NA	NA	YES	NA	NA	NA	Eye Dam. 1	Acute Tox. 2	NA	STOT SE 3	STOT RE 2
110-15-6	SUCCINIC ACID	1B	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	Asp. Tox. 1	NA	NA
71-55-6	METHYLCHLOROFORM	NA	2A	Inadequate information to assess carcinogenic potential		A4	NA	NA	NA		NA	List 2	NA	NA	NA	NA	NA	Acute Tox. 4	NA	NA	NA
13463-67-7	TITANIUM DIOXIDE	2	2B	NA		A4	NA	NA	NA		NA	NA	YES	NA	NA	NA	NA	NA	NA	NA	NA
77-90-7	ACETYLTRIBUTYL CITRATE	1A	NA	NA		NA	1B	NA	NA		NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

Appendix IV

Basic units in electricity

Voltage (V): Volts are a measure of the potential difference or the force that causes electrons to flow through a conductor.

Amperage is a way to measure the amount of electricity (volume) running through a circuit. Amps are a measure of current or the rate at which electrons flow past a given point. The larger the amperage, the more electricity can flow through the circuit.

Wattage (W) is the amount of power an electric device consumes (or the amount of work that an electrical current can do). Wattage is calculated by multiplying voltage (pressure/speed) with amperage (volume), expressed as V x A = W. The faster each electron moves through the circuit, and the greater the volume that the circuit can hold, the higher the wattage.

Resistance (R) is measured in ohms. Ohms are what makes it difficult for electrons to flow through a conductor. The higher the resistance, the more difficult it is for electrons to flow and the lower the current will be.

The three terms I (current or amperage), V and R relate is related as follows: $I = V/R$ (or $V = IR$) . This is known as Ohm's law.

Watts, volts, amps, and ohms are related to one another by the following equations: P = VI or I2R or V2/R

List of Tables

Table 1. E-liquid consumed as a function of changes in either watt, volt or temperature.

Study	Type of e-cigarette	E-liquid	Method	Results
Floyd et al., 2018	G2 tank-style EC atomizer (KangerTech Protank V1, Shenzhen, China). Variable voltage EC battery or a laboratory power supply Single coil (measured 3,02Ω)	Commercial: Cinnamon flavored, 24 mg/mL nicotine, estimated to be 2/3 PG and 1/3 VG	E-liquid vaporization measured by weighing before and after each session (mg/puff) Puff topography: 3s / 20 mL/ Power: 3 to 11.9 W	The authors derived the function for mass of e-liquid consumed for the watt range investigated: mg/puff consumed = 0.8786 x (watt) – 2.5436 E-liquid vaporization increased linearly with watt used (no statistical analysis). Cumulative mass distributions showed that with increasing watt, the mass of particles around 1000 nm was observed to increase. With increasing watt, an increase in micron sized particles and a decrease in nano-sized particles was observed.
Gillman et al., 2016.	1: CE4 single top coil 2.8 Ω tankstyle (Vision, Shenzhen, China). 2: Protank 1 Single bottom coil 2.7Ω (KangerTech, Shenzhen, China) 3: Gladius Dual bottom coil 2.8Ω (Innokin, Shenzhen, China) 4: Nautilus Single bottom coil 2.2 Ω (Aspire USA, Kent, WA) 5: SubTank Single bottom coil 0.72 Ω (KangerTech)	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	Weight difference after 25 puffs for the device (mg/puff) Puff topography: 4s / 55 mL Power: 1: 5.3 W – 9.2 W 2: 5.2 W – 9 W 3: 5.6 W – 9.7 W 4: 7.3 W – 12.6 W 5: 10 W – 25 W	The authors observed an increase in mg/puff with increasing watt used (based on average values reported), except for the two highest watts used for device 1 (no statistical analysis).
Jensen et al., 2017.	Innokin® iTaste VV4 (2.2 Ω), with a KangerTech® Protank-II clearomizer	Lab made: 1:1 VG/PG ratio.	The clearomizer was weighed before and after three puffs taken per sample. (mg/puff) Puff topography: 3s, 5s, 10s / 50 mL Power: 6 W-14 W	Linear trend, increasing mass consumed with increasing watt used (no statistical analysis).
Korzun et al., 2018	Variable voltage battery unit, (Tesla Invader III with two 18650 HG2 LG batteries (3.7 V, 3000 mAh)) and a KangerTech SubTank, single bottom coil, 1.26Ω Mini atomizer	Lab made: 1:1 VG/PG ratio.	Mass consumed of e-liquid was weighed before and after vaping. (mg/puff) Puff topography: 3s / 7 mL/s, 18.3 mL/s, 36 mL/s Power: 11- 35 W	A linear trend between increasing mass of e-liquid consumed and increasing watt was observed (no statistical analysis). The study also measured e-liquid consumed as a function of different flow rates. By increasing the flow rate, an increased consumption of e-liquid was reported.
Lee et al., 2020.	Starter Kit Q16, Justfog (1.6Ω), Korea, adjustable voltage	Commercial: 50 different e-liquids tested at each voltage.	Amount of liquid consumed. (mg) Recovery rate (approximately 94%) calculated from weight of Cambridge filter and weight of e-liquid consumed. Puff topography: 2/s / 16.67 mL/s Power: 3.4 V, 4 V, 4.8 V	An increase in voltage was associated with an increase in e-liquid consumed. (no post hoc analysis after one way ANOVA was perfomed).
Li et al., 2021	Evolv DNA 75 color modular vaping device (Evolv LLC., Hudson, Ohio) Single mesh (0.12Ω), stainless steel (SS316L, FreeMax Technology Inc., Schenzhen, China	Lab made: 30/70, PG/VG, 3 mg/mL nicotine.	Weighing the e-liquid compartment before and after 10 puffs. Total aerosol mass (mg/puff) Puff topography: 3s / 59.3 mL Temperature: 157°C, 191°C, 216°C, 246°C, 266°C	The results for all temperatures using the 30/70 PG/VG based liquid were presented graphically. Two temperatures and the amount of aerosol were presented. The mass of e-liquid consumed per puff (total aerosol mass), increased with increasing temperature used (no statistical analysis).
Pankow et al., 2017.	1: EVOD tank-type atomizer, 1.8 Ω single horizontal coil (Kangertech, Shenzhen, China). 2: Subtank NanoTM V.1 (Kangertech) 1.2 Ω, single vertical coil, tank-type atomizer.	Lab made: 1: PG:VG 2: PG:VG + benzoic acid 3: PG:VG, benzoic acid, nicotine 4: PG:VG, benzaldehyde 5: PG:VG, benzaldehyde and nicotine	E-liquid consumed, measured by weight loss of unit. (mg/puff) Calculated TPM (µg/m3) Puff topography: 5s / 50 mL Power: 1: 6 W, 13 W 2: 6 W, 13 W, 20 W, 25 W	The authors observed a trend that increased watt was associated with increased e-liquid consumption (for all e-liquid formulations, no statistical analysis).

Talih et al., 2021	SMOK®TF-N2 Air Core (0.22 Ω), an external power supply was used.	Lab made: 100 % propyleneglycol	E-liquid vaporized measured by change in mass of the ECIG tank before and after sampling (mg/15 puffs) Puff topography: 4s / 16.67 mL/s Power: 15 W – 80 W	Significant increase in liquid consumption with increasing watt used was reported.
Vreeke et al., 2018	1: SMOK Baby, 0.4 Ω, Q2, single vertical coil with a SMOK Alien 220W VV/VW/TC battery 2: Kanger Protank 2 Clearomizer, 2.2 Ω, M32 single horizontal coil with a SMOK Alien 220W VV/VW/TC battery	Lab made: 1:1 PG/VG. 10 % triacetin in 1:1 PG/VG	Mass of cartomizer before and after vaping. (g of liquid consumed) Puff topography: 3s / 55mL Power: 1: 55 W, 65 W 2: 9 W, 11 W	Calculated mean from three replicates presented in Supplementary information for PG/VG based liquid.No statistical analysis on mass of e-liquid consumed. SMOK Baby Watt mg/puff 55 38.19 65 40.40 Kangertech Protank 2 Watt mg/puff 9 6.91 11 11.2

Table 2. E-liquid consumed as a function of changes in either watt, volt, or temperature (details on results)

Authors	e-liquid	Puff topography	Power (volt/ watt/ohm/ temp)	Mass vaped (mg/puff)
Gillman et al., 2016.	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Single top coil	4s / 55 mL	5.3W, 2.8 Ω 6.5W, 2.8 Ω 7.8W, 2.8 Ω 9.2W, 2.8 Ω	4.1 6.2 7.4 7.1
Gillman et al., 2016.	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Single bottom coil.	4s / 55 mL	5.2W, 2.6 Ω 6.4W, 2.6 Ω 7.7W, 2.6 Ω 9.0W, 2.6 Ω	3.8 5.4 6.5 7.7
Gillman et al., 2016.	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Dual bottom coil	4s / 55 mL	5.6W, 2.8 Ω 6.9W, 2.8 Ω 8.2W, 2.8 Ω 9.7W, 2.8 Ω	1.5 3.9 5.5 6.9
Gillman et al., 2016.	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Single bottom coil	4s / 55 mL	7.3W, 2.2 Ω 8.9W, 2.2 Ω 10.6W, 2.2 Ω 12.6W, 2.2 Ω	2.3 4.3 6.7 9.4
Gillman et al., 2016.	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Single bottom coil	4s / 55 mL	10W, 0.72 Ω 15W, 0.72 Ω 20W, 0.72 Ω 25W, 0.72 Ω	7.5 15.0 22.0 28.0
Jensen et al., 2017	Lab made: 1:1 VG/PG ratio	3s / 50 ml	6W, 2.2 Ω 8W, 2.2 Ω 10W, 2.2 Ω 12W, 2.2 Ω 14W, 2.2 Ω	5.5 8.6 11.3 13.6 14.3
Jensen et al., 2017	Lab made: 1:1 VG/PG ratio	5s / 50 ml	6W, 2.2 Ω 8W, 2.2 Ω 10W, 2.2 Ω 12W, 2.2 Ω 14W, 2.2 Ω	10.1 14.2 17.4 18.1 19.1
Jensen et al., 2017	Lab made: 1:1 VG/PG ratio	10s / 50 ml	6W, 2.2 Ω 8W, 2.2 Ω 10 W, 2.2 Ω 12 W, 2.2 Ω 14 W, 2.2 Ω	15.7 16.6 18 19.5 21.9

Kozun et al., 2018	Lab made: 1:1 VG/PG ratio. Single bottom coil	3s – 7 ml/s	11 W, 1.26 Ω 13 W, 1.26 Ω 17 W, 1.26 Ω 24 W, 1.26 Ω 35 W, 1.26 Ω	4.74 6.05 11.38 13.25 14.78
Kozun et al., 2018	Lab made: 1:1 VG/PG ratio. Single bottom coil	3s – 18.3 ml/s	11 W, 1.26 Ω 13 W, 1.26 Ω 17 W, 1.26 Ω 24 W, 1.26 Ω 35 W, 1.26 Ω	7.27 8.99 16.50 18.50 20.43
Kozun et al., 2018	Lab made: 1:1 VG/PG ratio. Single bottom coil	3s – 36 ml/s	11 W, 1.26 Ω 13 W, 1.26 Ω 17 W, 1.26 Ω 24 W, 1.26 Ω 35 W, 1.26 Ω	9.58 14.20 19.97 28.30 39.96
Lee et al., 2000	Commercial: 50 different e-liquids tested at each voltage. Results presented as averages of the 50 products.	2s – 16.67 ml/s	3.4V, 1.60 Ω 4.0V, 1.60 Ω 4.8V, 1.60 Ω	4.4 5.51 6.83
Li et al., 2021	Lab made: 30/70, PG/VG, 3mg/mL nicotine. Single mesh, stainless steel coil	3s / 59.3 ml	191⌧, 0.12 Ω 274⌧, 0.12 Ω	26 135
Pankow et al., 2017	Lab made: 1:PG:VG 1: Single horizontal coil (1.8 Ω), tank type atomizer (EVOD) 2: Single vertical coil (1.2 Ω), tank type atomizer (Subtank Nano)	5s / 50 ml	6W, 1.8 Ω 13W, 1.8 Ω 6 W, 1.2 Ω 13 W, 1.2 Ω 20 W, 1.2 Ω 25 W, 1.2 Ω	6.8 12 0.5 8.1 17 24
Pankow et al., 2017	Lab made: 1: PG:VG + benzoic acid Single horizontal coil, tank type atomizer (EVOD) Single vertical coil, tank type atomizer (Subtank Nano)	5s / 50 ml	6W, 1.8 Ω 13W, 1.8 Ω 6 W, 1.2 Ω 13 W, 1.2 Ω 20 W, 1.2 Ω 25 W, 1.2 Ω	6.7 11 1.2 9.8 20 23
Pankow et al., 2017	Lab made: 1: PG:VG, benzoic acid, nicotine Single horizontal coil, tank type atomizer (EVOD) Single vertical coil, tank type atomizer (Subtank Nano)	5s / 50 ml	6W, 1.8 Ω 13W, 1.8 Ω 6 W, 1.2 Ω 13 W, 1.2 Ω 20 W, 1.2 Ω 25 W, 1.2 Ω	6.3 11 0.7 9.9 19 31
Pankow et al., 2017	Lab made: 1: PG:VG, benzaldehyde Single horizontal coil, tank type atomizer (EVOD) Single vertical coil, tank type atomizer (Subtank Nano)	5s / 50 ml	6W, 1.8 Ω 13W, 1.8 Ω 6 W, 1.2 Ω 13 W, 1.2 Ω 20 W, 1.2 Ω 25 W, 1.2 Ω	6.6 10 1.6 11 18 30
Pankow et al., 2017	Lab made: 1: PG:VG, benzaldehyde and nicotine Single horizontal coil, tank type atomizer (EVOD) Single vertical coil, tank type atomizer (Subtank Nano)	5s / 50 ml	6W, 1.8 Ω 13W, 1.8 Ω 6 W, 1.2 Ω 13 W, 1.2 Ω 20 W, 1.2 Ω 25 W, 1.2 Ω	6.8 11 0.8 9.6 19 24
Talih et al., 2021	Lab made: 100 % propylene glycol	4s / 16.67 mL/s	15W, 0.22 Ω 31 W, 0.22 Ω 50 W, 0.22 Ω 60 W, 0.22 Ω 70 W, 0.22 Ω 80 W, 0.22 Ω	3.11 18.48 30.9 38.65 41.95 49.3
Vreeke et al., 2018	Lab made: 1:1 PG/VG, 10 % triacetin in 1:1 PG/VG Single vertical coil	3s / 55 ml	55W, 0.4 Ω 65W, 0.4 Ω	38.19a 40.40a
Vreeke et al., 2018	Lab made: 1:1 PG/VG, 10 % triacetin in 1:1 PG/VG Single horizontal coil	3s / 55 ml	9W, 2.2 Ω 11W, 2.2 Ω	6.91a 11.2a

a Calculated mean from three replicates presented in Supplementary information for PG/VG based liquid

Table 3. Total particle mass identified by collecting aerosol filters as a function of changes in either watt, volt, or temperature.

Study	Type of e-cigarette	E-liquid	Method	Results
Lee et al., 2020.	Starter Kit Q16, Justfog (1.6Ω) Korea, adjustable voltage.	Commercial: 50 different e-liquids tested at each voltage.	Particle recovery rate, approximately 94%. Calculated from weight of Cambridge filter and weight of e-liquid consumed. Puff topography: 2s / 16.67 mL/s Power: 3.4 V, 4 V, 4.8 V	Particle mass collected on the filter increased with increasing voltage applied.
Li et al., 2021	Evolv DNA 75 color modular vaping device (Evolv LLC., Hudson, Ohio) with Single mesh (0.12Ω), stainless steel (SS316L, FreeMax Technology Inc., Schenzhen, China)	Lab made: 30/70, PG/VG, 3mg/mL nicotine.	Weighing the e-liquid compartment before and after 10 puffs. Total aerosol mass (mg/puff), particle mass on filter measured (mg/puff) Puff topography: 3s / 59.3 mL Power: 157°C, 191°C, 216°C, 246°C, 266°C	Some results presented graphically. The particle mass collected on filter increased with increasing temperature measured by the authors. However, the temperature set by the device was not well correlated with particle mass. Thus, it is important to actually measure the temperature of the device. (No statistical analysis)
Robinson et al., 2018.	Innokin iTaste MVP 2.0 vaporizer with Innokin iClear 30 dual coil tank (i30), 4 wicks per coil.	Commercial: AVAIL Tobacco Row (1.8 % nicotine)	Cambridge styler filter, gravimetrically Filter pad weighted before and after 10 puffs. The filter pad mass and the cumulative puff volumes were used to calculate whole aerosol mass concentrations (mg/mL). Puff topography: adjusted to give a total cumulative volume of 750 mL for 10 puffs. Power: 6 W, 7.5 W, 10 W	Results presented graphically. Increase in total particular mass concentration was observed with increasing watt used. Results presented with 95 % confidence intervals.
Son et al., 2018	Refillable tank type e-cigarette (The council of Vapor, Walnut, CA, USA) with a nichrome coil.	Lab made: VG based, 12mg/mL nicotine.	Mass of aerosol on Teflon filter weighted while in filter holder before and after aerosol collection. Puff topography: 3.8s / 90 mL Power: 6.4, 14.7 and 31.3W	Increase in particle mass collected on filter was observed with an increase in wattage.
Stephens et al., 2019	KangerTech CE4, top coil (1.8 Ω) KangerTech EVOD, bottom coil (1.8 Ω) KangerTech Subox Mini C (1.5 Ω), SSOCC atomizer	Lab made: 70:20:10 (PG/VG/Water)	Gravimetrically Aerosol trapped in silica wool plugs (mg/puff) Puff topography: 4s / 55mL. Power (only for KangerTec Subox): 10 -50 W	Some results presented graphically Mass of aerosol trapped increased linear with increasing watt used. The aerosol trapped with the KangerTech Subox Mini C was well correlated with power (watt).
Talih et al., 2015	V4L CoolCart (3.6 Ω) cartomizer	Commercial: e-liquid in pre-filled cartomizer	Total particulate matter was measured by weighing the filter pad and holder before and after each sampling session. Puff topography: 1: 4s / 17 mL/s 2: 4s / 33 mL/s 3: 8s / 17 mL/s 4: 8s / 33 mL Power:3.3 V, 5.2 V	An increased voltage was reported to have an significant effect on the amount of TPM.
Talih et al., 2020a	Kanger Subox (0.5 Ω, nichrome coil) Mini-C tank ECIG, powered using a DC power supply. Five power levels were used in the range 5–45 W	Lab made: 1: 100 % PG 2: 100 % VG, (nicotine 15mg/g freebase or protonated)	Total particulate matter (TPM) was determined by weighing the filter assembly before and after each session. (mg/15 puffs). Puff topography: 4s / 33 mL/s Power: 5W-45 W	There was an increase in TPM with increasing power (watt) used, both for protonated and free base nicotine. Only PG based e-liquid investigated at 5 W, as VG based e-liquid did not generate measurable amount of aerosol at this watt.
Talih et al., 2020b	1: SMOK®TF-N2 Air Core, (Vertical nickel coil, 0.12 Ω), VaporFi Platinum™ (VF). 2: SMOK® V12-Q4, with vertical coil (0.15 Ω Kanthal). 3: VF platinum with vertical nichrome coil (2.2 Ω). All coupled with a DNA200 circuit board, used to supply power.	Lab made: 1: 100 % PG 2: 100 % VG	Mass of liquid vaporized (TPM) was measured by weighing the glass fiber filter in its holder before and after each session. Puff topography: 4s / 16.67 mL/s Power: 1:15-30W 2:50-80W 3:1-20W	For all e-cigarettes investigated, the mass vaporized increased with increasing heat flux (kW/m2).

Table 4. Total particle mass identified by collecting aerosol on filters as a function of changes in either watt, volt, or temperature (details on results)

Authors	e-liquid	Puff topography	Power (volt/watt/ohm/temp)	Particulate mass on filter (mg/puff)
Lee et al., 2020	Commercial: 50 different e-liquids tested at each voltage. Results presented as averages of the 50 products.	2s - 16.67 mL/s	3.4V, 1.6 Ω 4.0V, 1.6 Ω 4.8V, 1.6 Ω	4.1a 5.2 6.4
Li et al., 2021	Lab made: 30/70, PG/VG, 3mg/mL nicotine. Single mesh, stainless steel coil	3s / 59.3 ml	191⌧, 0.12 Ω 274⌧, 0.12 Ω	3.9 14.1
Stephens et al., 2019	Lab made: 70:20:10 (PG/VG/Water) 1: KangerTec, bottom coil (EVOD) 2: KangerTec (Subox Mini)	4s / 55mL	13W, 1.8 Ω 15W, 1.8 Ω 10W, 1.5 Ω 15W, 1.5 Ω 30W, 1.5 Ω 50W, 1.5 Ω	7.54 5.66 5.32 9.46 23.6 46.6
Son et al., 2018	Lab made: VG based, 12mg/mL nicotine.	3.8 s / 90 mL	6.4Wb 14.7Wb 31.3Wb	1.47 8.9 21.3
Talih et al., 2015	Commercial: e-liquid in pre-filled cartomizer	4s / 17 mL/s	3.3V, 3.6 Ω 5.2V, 3.6 Ω	1.96 8.60
Talih et al., 2015	Commercial: e-liquid in pre-filled cartomizer	8s / 17 mL/s	3.3V, 3.6 Ω 5.2V, 3.6 Ω	4.70 20.84
Talih et al., 2015	Commercial: e-liquid in pre-filled cartomizer	4s / 33 mL/s	3.3V, 3.6 Ω 5.2V, 3.6 Ω	1.97 10.8
Talih et al., 2015	Commercial: e-liquid in pre-filled cartomizer	8s / 33 mL/s	3.3V, 3.6 Ω 5.2V, 3.6 Ω	4.59 22.21
Talih et al., 2020a	Lab made: 100 % PG (freebase nicotine, 15mg/g)	4s / 133.3 mL/s	5W, 0.5 Ω 10W, 0.5 Ω 15W, 0.5 Ω 30W, 0.5 Ω 45W, 0.5 Ω	1.17 10.27 20.65 48.1 62.77
Talih et al., 2020a	Lab made: 100 % PG (protonated nicotine, 15mg/g)	4s / 133.3 mL/s	5W, 0.5 Ω 10W, 0.5 Ω 15W, 0.5 Ω 30W, 0.5 Ω 45W, 0.5 Ω	1.17 11.23 23.09 49.92 63.75
Talih et al., 2020a	Lab made: 100 % VG (freebase nicotine, 15mg/g)	4s / 133.3 mL/s	10W, 0.5 Ω 15W, 0.5 Ω 30W, 0.5 Ω 45W, 0.5 Ω	0.48 3.98 36.48 53.3
Talih et al., 2020a	Lab made: 100 % VG (protonated nicotine, 15mg/g)	4s / 133.3 mL/s	10W, 0.5 Ω 15W, 0.5 Ω 30W, 0.5 Ω 45W, 0.5 Ω	0.21 8.29 33.4 52.9

Talih et al., 2020b	Lab made: 100 % PG TFN2, vertical coil	4s / 16.67 mL/s	15 W, 0.12 Ω	3.11
			31 W, 0.12 Ω	18.5
			46 W, 0.12 Ω	29.2
			50 W, 0.12 Ω	30.9
			60 W, 0.12 Ω	38.7
			62 W, 0.12 Ω	39.9
			70 W, 0.12 Ω	42.0
			77 W, 0.12 Ω	39.1
			80 W, 0.12 Ω	49.3
			90 W, 0.12 Ω	50.1
			93 W, 0.12 Ω	63.6
			100 W, 0.12 Ω	51.2
			110 W, 0.12 Ω	51.7
			120 W, 0.12 Ω	52.0
			130 W, 0.12 Ω	52.8
Talih et al., 2020b	Lab made: 100 % PG V12-Q4, vertical coil	4s / 16.67 mL/s	50 W, 0.15 Ω	44.4
			100 W, 0.15 Ω	107
			125 W, 0.15 Ω	136
			140 W, 0.15 Ω	138
			150 W, 0.15 Ω	138
			160 W, 0.15 Ω	152
			170 W, 0.15 Ω	135
Talih et al., 2020b	Lab made: 100 % PG V12-Q4, vertical coil	4s / 16.67 mL/s	1 W, 2.2 Ω	0.06
			3 W, 2.2 Ω	3.06
			4 W, 2.2 Ω	4.96
			5 W, 2.2 Ω	6.76
			6 W, 2.2 Ω	7.89
			7 W, 2.2 Ω	8.63
			8 W, 2.2 Ω	10.2
			9 W, 2.2 Ω	11.0
			11 W, 2.2 Ω	11.3
			13 W, 2.2 Ω	11.6
			15 W, 2.2 Ω	13.1
			20 W, 2.2 Ω	16.7

a Calculated from recovery rates

b Specific resistance (ohm) used for the experiment not reported.

Table 5. Gravimetrically derived size distributions (cascade impactors) as a function of changes in either watt, volt or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Bertrand et al., 2018	iStick 30 W, Eleaf, dual-coil atomizer 1.5Ω	Lab made: 1: 80/20 PG/VG 2: 20/80 PG/VG 3: PDO (1,3 propanediol)	Cascade impactor (Dekati® Low Pressure Impactor, 7nm to 10 µm) and gravimetrically. Puff topography: 4s / NR Power: 7 W, 10 W, 13 W (not clearly stated)	Increase in mass median aerodynamic diameter (MMAD) as a function of power. Results were reported graphically. However, the authors reported a linear function for MMAD as a function of watt for the different e-liquid combinations: 80/20 PG/VG: f(watt)=0.0083(watt)+0.7533 20/80 PG/VG: f(watt)=0.0233(watt)+0.6067
Dibaji et al., 2022	Reuleaux module ENDS (Wismec, Shenzhen, China) A: single Ni coil (0.15 Ω.) B: dual Ni coil (0.15 Ω.) C: single Ni coil(0.15 Ω.)	Lab made: 1: 35/65 PG/VG, 2: 50/50 PG/VG, 3: 35/65 PG/VG	High resolution ELPI (Dekati), 14 stages, (presented particle size range: < 0.1 µm, 0,1 – 1µm, > 1 µm). Puff topography: 3.5s / 55mL Power: 200°C and 300°C	Ultrafine particle fraction (< 0.1 µm): Atomizer C, a higher aerosol mass at 300°C compared to 200°C for the 65:35 PG:VG based e-liquid was reported (mg/puff). Fine particulate fraction (0.1 µm - 1 µm): Atomizer A (35:65 and 50:50 PG:VG) and atomizer B (50:50 PG:VG) at 300°C compared to 200°C, were reported to increase the particle mass (mg/puff). Coarse particle fraction (>1 µm): Atomizer A (35:65 PG:VG and 50:50 PG:VG) and B (50:50 PG:VG) at 300°C compared to 200°C, were reported to increase the particle mass (mg/puff).
Marocco et al., 2022	KangerTech (1.8 Ω) refillable cartridges T3S series clear cartomizer (Rock Bottom Vapes, LLC, Longwood, Florida)	Lab made: 43% PG, 50% VG, 5% Nicotine, 2% Menthol	Harvard compact cascade Impactor. Filters were weighed before and after sampling for the particle fractions: < 0.1 µm, 0,1 – 2.5µm, > 2.5 µm) Puff topography: 4s / 55 mL Power: 3.7V, 5V	Ultrafine particle fraction (< 0.1 µm): 3.7V, 80.62 mg/m3 5V, 25.7 mg/m3 Fine particulate fraction (0.1 µm - 1 µm): 3.7V, 579.33 mg/m3 5V, 208.99 mg/m3 Coarse particle fraction (>1 µm): 3.7V, 8.53 mg/m3 5V, 4.96 mg/m3
Mulder et al., 2019	AeroTank Clearomizer with a KangerTech atomizer (1.5 Ω, 1.8 Ω, 2.2 Ω) was used with an eGoV2 variable voltage battery	Lab made: 1:1 PG/VG 100% PG 100% VG, all with 12 mg/mL nicotine	10-stage micro-orifice uniform deposit impactor (MOUDI). Aluminum disks and filters were weighed before and after each session. Puff topography: NR Power: 3.9V, 4.3V, 4.7V	PG based e-liquid (MMAD): 3.9V, 4.3V, 4.7V (1.8 Ω), 0.644 µm 1.5 Ω, 1.8 Ω, 2.2 Ω, (4.3 V), 0.55 µm VG based e-liquid (MMAD): 3.9V, 4.3V, 4.7V (1.8 Ω), 0.377 µm 1.5 Ω, 1.8 Ω, 2.2 Ω (4.3 V), 0.417 µm 50:50 PG:VG based e-liquid (MMAD): 3.9V, 4.3V, 4.7V (1.8 Ω), 0.334 µm 1.5 Ω, 1.8 Ω, 2.2 Ω (4.3 V), 0.3389 µm Particle size distribution > 90 % between 0.172 – 1 µm
Pourchez et al., 2018	iStick 30 W, Eleaf, dual coil (1.5 Ω), atomizer (GS Air, Eleaf), 2200 mAh battery	Lab made: 1:80%/20%, PG/VG 2: 20%/80%, PG/VG	DLPI setup was used (Dekati LowPressure Impactor; Dekati Ltd., Finland). (7nm - 10µm). Puff topography: 4s / 500 mL/s (extracted only data from DLPI)	PG:VG (MMAD and mg/L aerosol) 20:80 PG:VG MMAD (µm) Output mg/L Watt 7 0.78 4.3 10 0.82 9.7 13 0.92 18.0 16 0.95 21.5 19 1.07 21.0 22 1.10 23.2 80:20 PG:VG MMAD (µm) Output mg/L Watt 7 0.81 5.0 10 0.84 6.7 13 0.86 14.0 16 0.87 15.0 19 1.02 19.5 22 1.19 18.6
Ranpara et al., 2021.	An automated e-cigarette aerosol generator (ECAG+e-Aerosols LLC, Central Valley, NY, USA) (did not use an e-cigarette) with 1.87 Ω	Lab made: 25 % PG, 73 % VG, 1% ethanol, 1 % water, 9.4 mg/mL benzoic acid.	MiniMOUDITM (MSP Corporation, Shoreview, MN, USA). Mass of aerosol on aluminum filter weighed for each stage. Particle size range: 0.056 – 10 µm. Puff topography: 4s / 55 mL, 65 mL, 75 mL Power: 6.5 and 7.5W	No significant effect of changes in watt on MMAD (µm). However, at 7.5 W increasing the puff volume to 75 mL from 55 mL lowered the MMAD significantly. MMAD with puff volume and 55, 65 and 75 ml respectively: 6.5 W: 1.10 µm, 1.11 µm, 1.10 µm 7.5 W: 1.23 µm, 1.13 µm, 1.02 µm
Zhao et al., 2018b	Brand A	Commercial: Tobacco flavor	Harvard Compact Cascade Impactor (CCI), gravimetrically. Filter weighed before and after sampling. Presented particle size range: < 0.1 µm, 0,1 – 2.5µm, > 2.5 µm – 10 µm. Puff topography: 4s / 55 mL Power: 3.7 , 4.8 and 5.7V	The authors observed an increase in total particulate mass as a function of increasing volt, where the fine particulate fraction represented the largest mass fraction. Results were presented graphically. We were, therefore, not able to extract the exact numbers for the different particle fractions presented

Table 6. Real time particle size distribution investigated as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Dibaji et al., 2022	Reuleaux module ENDS (Wismec, Shenzhen, China), A: single coil, Nickel 200, 0,15 Ω B: dual coil, Nickel 200, 0,15 Ω C: single coil, Nickel 200, 0,15 Ω	Lab made: 1: 35/65 PG/VG, 2: 50/50 PG/VG, 3: 65/35 PG/VG	High resolution ELPI (Dekati), 14 stages cascade impactor, and real time particle size distribution. Puff topography: 3.5s / 55mL Power: 200°C, 300°C	A multi-modal size distribution was observed. For atomizer A, three modes were observed: around 12 nm, 40 nm and 200–300 nm. For atomizers B and C a bimodal distribution was observed, with modes at 12 nm and > 500 nm. For the ultrafine particle fraction increasing temperature from 200°C to 300°C, resulted in higher particle number concentrations of atomizer C for the 65:35 PG:VG based e-liquid.
Floyd et al., 2018	G2 tank-style EC atomizer (KangerTech Protank V1, Shenzhen, China). Single coil (3,02 Ω) Variable voltage EC battery or a laboratory power supply	Commercial: Cinnamon flavored, 24 mg/mL nicotine, (2/3 PG and 1/3 VG)	Scanning Mobility Particle Sizer (SMPS) (16 – 583 nm). Aerodynamic Particle Sizer (APS) both from TSI (514nm – 19,8µm.). Puff topography: 3s / 20 mL/s Power: 3 W - 11.9 W	Trimodal particle size distribution was observed with modes of 20 nm, 200 nm and 1000 nm, and a possible mode over 20000 nm(possibly larger liquid droplets). With increasing watt used, an increase in micron sized particles was observed and a decrease in nano-sized particles. The mass particle distribution showed a peak at 1000 nm. The cumulative mass distributions showed that with increasing watt, the mass of particles around 1000 nm was observed to increase.
Ganguly et al., 2020	Open system device (0.3 Ω)	Commercial: 1: raspberry, orange, lemon and lime, +/- nicotine. 2: ripe strawberry, sweet apples and tart kiwi, +/- nicotine.	Portable laser spectrometer (model Mini-LAS 11R; GRIMM, Aerosol Technik) (0,25 - 32µm). Puff topography: 3s / 40 mL Power: 20 W,40 W, 55 W	Increase in particle number concentration with increasing watt. However, for one of the e-liquids no change in numbers between the two highest watts investigated (40 and 55 watt). Particle size distribution showed a peak mode at approximately 0.58µm for all watts and e-liquids investigated
Lechasseur et al., 2019	Joyetech eVIC-VTC Mini 1: 0.5 Ω stainless steel range: 15 W–60 W 2: 1.5 Ω stainless steel range: 10–25 W 3: 0.15 Ω nickel range: 70 W	Lab made: 1:1 VG/PG ratio.	Condensation Particle Counter (CPC 3787, TSI Inc.) and a SMPS (TSI 3080, TSI Inc, 20.9nm - 881.7 nm). Puff topography: 4.2s / 70 mL Power: 1: 24 W, 37.5W, 51 W 2: 13.2 W, 18 W, 22.8 W 3: 70W	A significant increase in particle size with increasing watt applied was reported. An, except was noted for 18 watts compared to 13.2 watt for the 1.5 ohm coil. An increase in temperature had a significant effect on the particle size distribution. An increase in the smallest particles was observed at 250°C compared to 210°C and 225°C with a 0.15 ohm coil at 70W. The PG:VG ratio, flavor and nicotine content may affect the particle size distribution.
Marocco et al., 2022	KangerTech (1.8 Ω) refillable cartridges T3S series clear cartomizer (Rock Bottom Vapes, LLC, Longwood, Florida)	Lab made: 43% PG, 50% VG, 5% Nicotine, 2% Menthol.	NanoScan SMPS (TSI 3910, 10 nm – 420nm, TSI Inc., Shoreview, Minnesota). Aerodynamic particle sizer spectrometer (APS, Model 3321; TSI Inc.). (0.5µm - 20µm) Puff topography: 4s / 55 mL Power: 3.7V and 5 V	The nano particle number concentration decreased with increased voltage used. The micro particle number concentrations increased with increased volt used. Total particle number 0.5 - 20 µm and mode: 3.7V, 4052/cm3, 1.08 µm 5V, 7048/cm3, 1.03 µm Total particle number 10 – 420 nm µm and mode: 3.7V, 6.45x106/cm3, 96.71 nm 5V, 5.2x106/cm3, 87.94 nm
Son et al., 2020b	Cartomizer with 0.8 - 2.0 Ω, nichrome coils (The Council of Vapor, Walnut, CA, USA) with adjustable air hole (1–2 mm in diameter). Sigelei-100-W battery (Sigelei US, Pomona, CA, USA	Lab made: VG, nicotine (12 mg/mL	Portable aerosol mobility spectrometer (PAMS, KANOMAX USA, Andover, NJ) and an optical particle counter (OPC, model 3886, KANOMAX USA, Andover, NJ). (10 nm – 5 µm) Puff topography: 3.8s / 90 mL Power: 6.4 W (130.6 °C), 14.7 W (199.1 °C), 31.3 W (223.9 °C)	Count median diameter was reported to be significantly higher at 31.3 W (228 nm), compared to at 6.4 W (200 nm). No significant difference was observed for the calculated mass median diameter based on the density of the e-liquid. The authors reporter significant higher particle number concentration at 31.3 W (7.2x108) compared to 6.4 W (1.42x108). The authors also reported that the base materials PG, VG, puff duration and volume affected the particle size distribution.
Zhang et al., 2023	VOOPOO DRAG 2 1: with 0.6 Ω coil 2: with 0.2 Ω coil	Commercial: Tobacco 3 (American Patriots), 35/65 VG/PG	SMPS (TSI 3080 and 3786, 7 nm – 300 nm). Optical particle sizer (OPS, TSI 3330, 0.3 µm – 10 µm). Particle emission per puff measured in chamber. Emission per/puff (µg/puff) was calculated for particle number and mass, assuming spherical particles with density of 1 g/cm3. Puff topography: 4s / 55mL Power: 1: 22W and 29W 2: 45W and 63W	Particles measured in a chamber (6 m3). No statistical significant difference in number of particles or mass for the 0.6 Ω coil at 22 or 29 W, or the 0.2 Ω coil at 45 or 63 W.

Zhao et al., 2018b	Brand A	Commercial: Tobacco flavor	SMPS (TSI 3910, 10 nm –420 nm, TSI Inc., Shoreview, MN, USA) and the aerodynamic particle sizer (APS, Model 3321, TSI Inc., Shoreview, MN, 0.5 to 20 µm). Puff topography: 4s / 55mL Power: 3.7V, 4.8V, 5.7V	Bimodal particle size distribution reported. The modal particle diameter for the mode with the largest particle diameter, seemed to increase with an increase in volt applied

Table 7. Particle emissions related to other factors (coil ageing/puff number)

Study	**Type of e-cigarette**	**E-liquid**	**Method**	**Properties investigated and results**
Jeon et al., 2023	Juul	Commercial: Juul Virginia tobacco 5%.	The first 1–50 puffs and the 101–150 puffs were. characterized with a mobility particle sizer (SMPS, models TSI 3080 and 3786), (size range: 7–300 nm) and an optical particle sizer (OPS, model TSI 3330), (size range: 0.3–10 µm)	The particle concentration and size were investigated as a function of coil aging (two puff fractions). Both the concentration (mg/m3) and the geometric mean particle diameter (GMD) increased between the two puff fractions (1-50 and 101-150 puffs). 1 – 50 puffs, 0.00212 mg/m3, 0.715 µm 101 – 150 puffs, 0.135 mg/m3, 0.902 µm
Saleh et al., 2021	Vuse ALTO,	Commercial: Labelled, 5% nicotine	Total particulate matter and change in pod mass was performed by weighing the filter and the pod before and after each session. Puff flow rate 18.3 mL/s and duration of 5.5s.	The authors investigated the amount of e-liquid consumed and total particulate matter over the lifetime of the pod (N = 15), until failure (sharp increase in coil resistance, reported to be between 135 to 215 puffs). The e-liquid consumed and TPM was constant until failure for all "light" colored e liquids, while for the "dark" colored e-liquids a linear decrease in TPM was observed. The reason for the dark colour is not known.
Zhang et al., 2023	JUUL (7 W, 2 Ω) VOOPOO DRAG 2 (45 W and 0.2 Ω or 63 W 0.2 Ω, or 22 W and 0.6 Ω or 29 W and 0.6 Ω)	Tobacco flavored, 5% nicotine Tobacco flavored, 0.3% nicotine	Scanning mobility particle sizer (SMPS, models TSI 3080 and 3786). (Size range, 7 nm – 300 nm). Optical particle sizer (OPS, TSI 3330). (Size range, 0.3 µm – 10 µm). Particle emission per puff measured in chamber. Emission per/puff (µg/puff), was calculated for both particle number and mass, assuming spherical particles with density of 1 g/cm3	The authors investigated the particle number concentrations and mass as a function of the puff fractions: 1-50, 51 – 100 and 101-150. The results were presented graphically. The authors reported for the pod type e-cigarette a small decrease in particle number concentrations and mass with an increasing puff fraction. However, the reductions were not significant. For the mod-types investigated, no clear pattern was observed for changes in particle number concentrations or mass as a function of increased number of puffs. The experiments for the mod-types were only performed with N=1.

Table 8. Particle emissions related to other factors (removing and re-inserting the pod during puff cycles)

Study	Type of e-cigarette	E-liquid	Method	Properties investigated and results
Soule et al., 2022	Juul	Commercial: Tobacco flavour, 5% nicotine	Concentrations of particles ≤ 2.5 µm in diameter were measured using the pDR-1500 monitor (pDR 1500, Thermo Scientific, Franklin, MA) in a 0.5 m3 chamber. Puff topography: 3s/25 mL/s	The authors investigated the effect of removing and re-inserting the pod during a 10 puff cycle. Without re-inserting the pod, the level of PM2.5 was highest initially, and leveled off after 5 puffs Removing and re-inserting the pod kept the PM2.5 level at a higher concentration than without removing an re-inserting the pod.

Table 9. Particle emissions related to other factors (total particular matter as a function of interdrip interval)

Study	Type of e-cigarette	E-liquid	Method	Properties investigated and results
Talih et al., 2016	DDA (NHALER 510 Atomizer, 2.5 Ohms) powered by eGo-T battery (3.4V, Joyetech)	Commercial: Liquid Express, WaterMelon Chill, nicotine, 0 or 18 mg/mL	Total particulate matter was determined by weighing a filter. Puff topography: 8s/19.1 mL/s	The authors investigated the mass of the total particular matter (TPM) as a function of interdrip interval (the interval between dripping e-liquid directly on the coil) under a direct dripping regime. The authors reported that when increasing the interdrip interval a lower level of TPM over four puffs was collected.

Table 10. Nicotine in aerosol as function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Dusautoir et al., (2021)	Lounge model with a 2.8 Ω nichrome coil, and third generation ModBox model with a0.5 Ω kanthal coil	Propylene glycol <65%; glycerol <35%; food flavourings; nicotine 16 mg/mL	Nicotine collected in glass impingers. Puff topography: 2s / 55 ml Power: 4.6W (Lounge), 18W, 30W (ModBox)	The emission of nicotine (µg/puff) from the "ModBox" increased as a function of wattage
Floyd et al., (2021)	Evolve DNA-75 research electronic cigarette coupled with the Tobeco Super Mini Atomizer with 0.5 Ω coil	70% volume VG, 30% volume PG and 12 mg/mL nicotine	EC aerosol was drawn by negative pressure into bubblers (with coarse fritted glass diffusers and methanol as the collection solvent). Analyzed by GC-MS Puff topography:3.2s / 58.7-320 ml Power: 25-75W	Nicotine yield increased with both the vaping power and the puff flow rate
Gholap et al., 2021	DOVPO Trigger 168 W TC Box mod with 0.2 Ωs, stainless steel coil	E-liquids with 50 mg/ml nicotine and nicotine salts and nicotine salts in each flavor. Various ratios of PG/VG (100:0, 70:30, 30:70, 0:100 v/v) of PG:VG.	Generated aerosol was captured on a Cambridge filter. Nicotine analyzed by HPLC. Puff topography:3s / 55 ml Power: 90 and 120W	The freebase nicotine yield in the aerosol was dependent on nicotine form used in the e-liquid and wattage
Lee et al., (2020)	Starter Kit Q16, Justfog, Korea with 1.6 Ω coil.	50 different commercia e-liquids	Aerosol sampled by anautomatic sampling device onto 44 mm Cambridge filter Analyed by GC-FID Puff topography:2s / 1 L/min Power: 3.4-4.8V	The consumption of e-liquid increased as a function of voltage, but the amount of nicotine in the aerosol was similar irrespectively of voltage

Li et al., 2021	Evolv DNA 75 color modular vaping device with SS316L, 0.12 Ω FreeMax coil.	PG:VG 30:70, 3 mg/mL nicotine.	Particles were collected on hydrophilic polytetrafluoroethylene (PTFE) membrane filters, nicotine analyzed by GC-MS Puff topography:2-4s / 59.5 ml (3s) Power: 191 and 274□	Similar amount of nicotine per puff in aerosol at coil temp of 191 and 274□
Peace et al., 2018	KangerTech AeroTank e-cig with Nichrome coil (1.8 Ω), 2-mm diameter silica string as wick.	A 12-mg/mL nicotine in 50:50 propylene glycol (PG):vegetable glycerin (VG)	The aerosol was trapped in a simple glass assemblage and analyzed by a 3200 Q Trap HPLC–MS-MS. Puff topography: 4s / 2.3 L/min Power: 3.9-4.7V	Nicotine yield per puff increased with increasing voltage.
Sleiman et al., (2016)	EFO eGO with CE4 vaporizer with 2.6 Ω coil	Three commercial liquids, with approximately 40% PG, 40% VG and 15% ethanol, and 20-30 mg/ml nicotine (measured in study)	Aerosols were collected onto DNPH cartridges and VOC sorbent tubes. Nicotine analyzed by head space GC/MS. Puff topography: 5s / 50 mL Power: 3.8 and 4.8V	No trend in nicotine emission was observed with increasing voltage
Son et al., 2018	A refillable tank type of e-cigarette with 0.8-Ω, Nichrome heating coils (dual bottom-coil	100% VG + 12 mg/ml nicotine	E-vapor were collected on a 47 mm Teflon filter (2.0 μm pore size, Pal life sciences, Port Washington, NY, USA). Nicotine was analyzed by UV absorbance 260 nm. Puff topography: 3.8s / 91 mL Power: 6.4-31.3W	Nicotine emission increased with increasing wattage concomitant with an increased e-vapor mass. Yield (nicotine per mass unit) was highest at 14.7W.
Talih et al., (2015)	V4L CoolCart cartomizers, with 3.6 ± 0.16 Ω coil at 22 °C	The composition of the V4L liquid vehicle was assumed to be 80/20 PG/VG, with 8 and 16 mg/ml nicotine	The mouth end of the ECIG cartridge was connected by a 5-cm long Tygon® tube (ID) to a polycarbonate filter holder that contained a Gelman type A/E 47-mm glass fiber filter. Nicotine was analyzed by GC/MS Puff topography: 2-8s / 66-268 mL Power: 3.3 (3.0W) and 5.2V (7.5W)	Nicotine yield in the aerosol increased with increasing wattage concomitant with increased aerosol mass.
Talih et al., 2017a	VF tanks (2.4 Ω) and refillable unbranded (NB) dual-coil cartomizers (1.6 Ω).	100% PG with 8 mg/ml nicotine	For each experiment, the mouth end of the ECIG cartridge was connected to a polycarbonate filter holder that contains a Gelman type A/E 47 mm glass fiber filter. Nicotine was analyzed by GC-MS Puff topography: 4s / 1 L/min Power: 2-8W	Nicotine flux (the rate of which nicotine is emitted from the e-cigarette per unit time) increased with increasing wattage concomitant with increased aerosol mass

Talih et al., 2020a	Kanger Subox Mini-C tank ECIG with 0.5 Ω SSOC nichrome coil	100% PG and 100% VG with free base nicotine and protonated nicotine (15 mg/ml)	The ECIG cartridge was connected to a polycarbonate filter holder that contains a Gelman type A/E 47 mm glass fiber filter. Nicotine was analyzed by GC-MS Puff topography: 4s / 8 L/min Power: 5-45W	The yield was higher when PG was used as liquid. Nicotine yield was not influenced by nicotine form.
Uchiyama et al., (2020)	Three brands, variable wattage	E-liquid consisting of PG (30%), and VG, (70%), nicotine (0.3%), menthol, and apple flavor.	Sampled onto Cambridge filter pads (CFPs) for analysis of particulate matter followed by CX-572 cartridge for gas analysis. GC/MS, and LC photodiode array detector. Puff topography: 3s / 55ml Power: 10-75W	Nicotine in the aerosol increased with increasing wattage.

Table 11. Nicotine in aerosol as function of changes in either watt, volt, or temperature (details on results)

Authors	e-liquid	Volt/Watt/Ohm	Nicotine (µg/puff)	Mass vaped (mg/puff)	Nicotine (µg) pr mg mass vaped
Dusautoir et al., 2021	PG <65%; G <35%; food flavourings; nicotine, 16 mg/mL	18 W, 0.5 Ω 30 W, 0.5 Ω	60 µg/p 137 µg/p	NR (Not Reported)	NA (Not Applicable)
Floyd et al., 2021	70% VG, 30% PG, 12 mg/mL nicotine. Results presented as average of different flow rates (1.1 l, 3.0, 4.5, 6.0 l/min).	25 W, 0.5 Ω 50 W, 0.5 Ω 75 W, 0.5 Ω	96.3 276 369	12.1 43.2 62.3	7.96 6.32 5.81
Lee et al., 2020	50 different commercial e-liquids. Results presented as averages of the 50 products.	3.4 V, 7.2 W 4.0 V, 10 W 4.8V, 14.4 W	34 41 50	4.40 5.51 6.83	7.73 7.44 7.32
Li et al., 2021	PG:VG 30:70, nicotine 3 mg/mL	191 ☒ 274 ☒	7 10	3.9 14.1	1.79 0.71
Peace et al., 2018	12 mg/mL nicotine in 50:50 PG:VG	3.9 V, 1.8 Ω 4.3 V, 1.8 Ω 4.7 V, 1.8 Ω	88 91 125	NR	NA
Sleiman et al., 2016	PG:VG (50:50), 18 mg/ml nicotine (commercial liquid).	3.8 V, 2.6 Ω 4.8 V, 2.6 Ω	122 161	5.1 7.1	23.9 22.7
Son et al., 2018	100% VG + 12 mg/ml nicotine	6.4 W 14.7 W 31.3 W	16.3 137 236	1.47 8.9 21.3	11.1 15.4 11.1
Talih et al., 2015	V4L liquid 80/20 PG/VG + 8.5 mg/ml nicotine	3 W, 3.3 V 7.5 W, 5.2 V	20.0 78.7	1.96 (17 ml/sec) 8.55 (17 ml/sec)	10.2 9.2
Talih et al., 2015	V4L liquid 80/20 PG/VG + 8.5 mg/ml nicotine	3 W, 3.3 V 7.5 W, 5.2 V	19.3 100	1.97 (33 ml/sec) 10.2 (33 ml/sec)	9.8 9.8
Talih et al., 2020a	100% PG with free base nicotine	5 10 15 39 45	20.7 131 271 707 880	1.17 10.3 20.6 48.1 62.8	17.7 12.7 13.2 14.7 14.0

Talih et al., 2020a	100% PG protonated nicotine.	5 10 15 39 45	20.7 145 299 688 927	1.17 11.2 23.1 49.9 63.8	17.7 12.9 12.9 13.8 14.5
Talih et al., 2020a	100% VG with protonated nicotine	10 15 39 45	20.7 82 351 492	0.21 3.68 33.4 52.9	98.6 22.3 10.5 9.30
Talih et al., 2020a	100% VG with free base nicotine	10 15 39 45	18 72.7 371 459	0.48 3.98 36.5 53.3	37.5 18.3 10.2 8.61

Table 12. Nicotine emissions related to other factors (nicotine emission as a function of interdrip interval)

Study	Type of e-cigarette	E-liquid	Method	Properties investigated and results
Talih et al., 2016	DDA (NHALER 510 Atomizer, 2.5 Ohms) powered by eGo-T battery (3.4V, Joyetech)	Commercial: Liquid Express, WaterMelon Chill, nicotine, 0 or 18 mg/mL	Aerosol was drawn through a glass fiber filter (Gelman Type A/E 47 mm). Nicotine was extracted from the filter and analyzed by gas GC-MS. Puff topography: 8s/19.1 mL/s	Interdrip interval, i.e. the number of puffs between directly applying new e-liquid onto the coil, affected the nicotine concentration in the aerosol. The authors reported a reduced nicotine concentration after 15 puffs, when the interdrip interval increased from two to four. This indicates that less e-liquid is available to evaporate at later puffs, when the inter drip interval is increased

Table 13. Nicotyrine levels as a function of changes in watt, volt, or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Sleimann et al., 2016	eGo CE4, with a 2.6 Ω coil.	Classic tobacco, Apollo. PG:VG 50:50, nicotine 18 mg/mL	Volatile carbonyls in aerosols were. determined using 2,4-dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges (Waters Corp., United States), extracted, and analyzed using HPLC with UV detection (Agilent 1200). Puff topography: 5s / 50 mL/s Power: 3.8V and 4.8V	The authors investigated the amount of nicotyrine formed as a function of change in volt. Samples were retrieved both at the initial 5 first puffs and between the 30th to 40th puff, as the temperature of the aerosol increased until the temperature profile of the vapor leveled off around puff 30. The emission of nicotyrine was lower per mg e-liquid consumed at the initial sample (3.5 and 2.0 µg/mg at 3.8 and 4.8 V respectively) compared to the sample retrieved at a steady vapor temperature (6.3 and 6.1 µg/mg at 3.8 and 4.8 V respectively)

Son et al., 2018	Refillable tank type (The Council of Vapor, Walnut, CA, USA) was used. Two types of batteries: Apollo Valiant battery (Apollo e-cigarette, Concord, CA, USA) and Sigelei-100W battery (Sigelei US, Pomona, CA, USA) with adjustable Nichrome heating coils (0.8–2.0 Ω, dual bottom-coil)	Lab made: VG based e-liquid, 12 mg/mL nicotine	UV absorbance (GENESYS 10 UV–vis spectrophotometer, Thermo Scientific, Waltham, MA, USA) Puff topography: 3.8s / 90 mL/s Power: 6.4, 14.7 and 31.3 W	The authors reported a significant increase in nicotyrine concentrations in the aerosol as a function of watt. 6.4 W, 2.11 µg/puff nicotyrine 14.7 W, 12.7 µg/puff nicotyrine 31.3 W, 11.6 µg/puff nicotyrine 6.4 W, 1.4 µg/mg nicotyrine per mass vaped 14.7 W, 1.4 µg/mg nicotyrine per mass vaped 31.3 W, 0.54 µg/mg nicotyrine per mass vaped The amount of nicotyrine was unchanged when adjusted for mass vaped for the two lowest wattages, and decreased compared to the other wattages for the highest watt applied.

Table 14. Nicotine PG adduct levels as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Yan, 2021	SMOK Alien 220 Mod device (Shenzhen IVPS Technology Co, Shenzhen, China), with TFV8 Baby Tank with SMOK V8 Baby-Q2 coil.	Commercial: Pale Whale Vixen's Kiss (Pale Whale, Baldwin Park, CA), 20% PG / 80% VG, 6 mg/mL nicotine	Thermo Scientific LTQ-Orbitrap XL mass spectrometer Puff topography: 4s / 16.7 mL/s Power: 40, 120 and 200 W.	The authors were not able to quantitate the amount of nicotine-propylene glycol adduct (NIC-PG) due to lack of a standard. The authors reported, however, an association between watt applied and NIC-PG formation from the ratio of the peak area between NIC-PG and nicotine. The authors observed a steep increase in the ratio from 40 W to 120 W.

Table 15. VOC in aerosol as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid and VOC reported	Method	Results
Dusautoir et al., 2021	"Lounge" model with 2.8 Ω nichrome and third generation "ModBox" with 0.5 Ω coil, from NHOSS	Propylene glycol <65%; glycerol <35%; food flavourings; nicotine 16 mg/mL Reported VOC: Acetaldehyde, Propanone, Propanal, Methyl vinyl ketone, Crotonaldehyde, Methyl ethyl ketone, Methylpropenal, Butanal, Benzaldehyde, Isopentanal, Pentanal, Glyoxal, o-Tolualdehyde, m-Tolualdehyde, p-Tolualdehyde, Methylglyoxal, Hexanal, 2,5-Dimethylbenzaldehyde	Sep-Pak DNPH-Silica Plus Short Cartridges, UHPLC System with UV/VIS Detector temp Puff topography: 2s / 55 ml (CRM81) Power:18W and 30W	The low wattage "Lounge" model emitted less VOCs per puff than the "ModBox" device operated at 18 and 30 watts. The emission of VOCs from the "ModBox" increased with increasing wattage.
El-Hage et al., 2020	Kangertech ECIG device with Stainless steel organic cotton coils, and a nichrome coil (0.50 Ω resistance) (the Sub-Ohm MiniBox),	Nicotine benzoate salt dissolved in PG/VG ratios of 30/70, 50/50, and 0/100. Phenol, o-cresol, m-cresol, p-cresol, Reported VOC: Catechol, Resorcinol, Hydroquinone	Aerosols were trapped on 47 mm quartz filters, phenols analyzed on GC-MS. Puff topography: 1-4s, 5-12 L/min. Power: 15W, 30W, and 45 W	Increasing power and puff duration significantly increased all phenol emissions, while flow rate had no significant effects
El-Hellani et al., 2022	Kangertech Subox Mini e-cigarette	1-5% sucralose in PG/VG ration of 30/70 Reported VOC: Formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methacrolein, glyoxal, methylglyoxal, phenol and catechol.	Aerosols were trapped on 47 mm quartzfilters and VOCs analyzed on GC/MS. Puff topography: 4s, 8L/min. Power: 30W and 45W	Emission of VOC increased with increasing wattage

Geiss et al., 2016	Third generation e-cigarette with variable voltage/ wattage heating element with 1.6 Ω	Commercial, reported to be composed of glycerol (50%), propylene glycol (40%), water (6%), tobacco fragrance (3%) and nicotine (0.9%). Reported VOC: Formaldehyde, acetaldehyde and acrolein	Direct trapping on DNPH sorbent, HPLC Puff topography: 3s /50 ml Power: 5-25W	The authors reported a general increase in carbonyl emissions with increasing wattage (and thereby increased coil temperature). Dry coil temperature increased with increasing power output from 380 ℃ at 5 W up to 800 and 950 ℃ at 20 and 25 W respectively. Coil temp with liquid drenched wick was reported as lower at 5W and that temperatures increased with increasing number of puffs (approximately 100 ℃ in difference between first and last (fifth) puff at 20 W
Gillman et al., 2016.	1: CE4 single top coil 2.8 Ω tankstyle (Vision, Shenzhen, China). 2: Protank 1 Single bottom coil 2.7Ω (KangerTech, Shenzhen, China) 3: Gladius Dual bottom coil 2.8Ω (Innokin, Shenzhen, China) 4: Nautilus Single bottom coil 2.2 Ω (Aspire USA, Kent, WA) 5: SubTank Single bottom coil 0.72 Ω (KangerTech)	Lab made: 48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine. Reported VOC: Formaldehyde, acetaldehyde, acrolein	Aerosols collected in DNPH trapping solution. VOC analysed by HPLV-UV detection. Puff topography: 4s / 55 mL Power: 1: 5.3 W – 9.2 W 2: 5.2 W – 9 W 3: 5.6 W – 9.7 W 4: 7.3 W – 12.6 W 5: 10 W – 25 W	The amounts of carbonyls in aerosol per puff increased with increasing watt. On mass basis, three of the devices showed an increase in total aldehyde yield with increasing power applied to the coil, while two of the devices showed the opposite trend.
Jensen et al., 2015	"Tank system" e-cigarette featuring a variable voltage battery	e-liquid Halo "café mocha" flavor, 6 mg/ml of nicotine Reported VOC: Formaldehyde hemiacetal (FRA)	FRAs were identified by means of NMR Puff topography: 3-4s / 50ml Power: 3.3V and 5.0V	Aerosol from E-cigarette operated at high voltage contained formaldehyde hemiacetal, whereas this was not observed at low voltage.
Jensen et al., 2017	KangerTech® Protank-II clearomizer with a bottom heating coil (1.8–2.5).	1:1 v/v PG:VG solutions Formaldehyde hemiacetals, glycidol, enols and aldehydes	NMR for e-cigarette aerosol product identification Puff topography: 3-5s / 50ml Power: 4-15W	The intensities of novel aerosol product peaks in an NMR spectrum were proportional to the power delivered to the e-cigarette coil (increased intensity of aerosol peaks with increasing watts).
Li et al., 2021	Third generation Evolv DNA 75 color modular vaping device (Evolv LLC., Hudson, Ohio)	E-liquid nicotine concentration of 3 mg/mL, PG:VG ratio of 30:70 by volume. Reported VOC: Carbonyls including formaldehyde, acetaldehyde and acrolein.	Carbonyls and Organic Acids Characterized by (HPLC-HRMS). Volatile/Semivolatile PG and VG Characterized by a Chemical Ionization Triple-Quadrupole Mass Spectrometer (CIMS) Puff topography: 2-4s Power: 157-274 ℃	Amounts of carbonyls in aerosol per puff increased with increasing temperature.
Marrocco et al., 2022	KangerTech refillable cartridges T3S series clear cartomizer 1.8 Ω	5% Nicotine + 43% PG + 50% VG+ 2% Menthol Reported VOC: Total VOC (tVOC)	tVOC levels were measured, using a photoionization detector sensor, equipped with a sensitive ppb-level probe. Puff topography: 4s / 55 ml. Power: 3.7V and 5V	Gaseous VOC in aerosols from e-liquid was measured as function of voltage. No difference in tVOC emission was observed
Ogunwale et al., 2017	EVOD2 with coil resistance 1.5 Ω made by KangerTech	Halo Menthol Ice + 6 mg/ml nicotine Reported VOC: Acetaldehyde, acrolein, formaldehyde, acetone, propionaldehyde, butyraldehyde	GC/MS of carbonyls and NMR of Hemiacetals Puff topography: 4s / 91 ml. Power: 11.7, 14.7, 16.6W	Emission of all the analyzed VOC increased with wattage. Highest concentrations were observed for acetaldehyde, formaldehyde, and acetone
Pankow et al., 2017	EVOD, Kangertech 1.8 Ω single horizontal coil with silica wick. Subtank Nano, Kangertech 1.2 Ω OCC single vertical coil with cotton wick	PG + GL (1:1). PG/VG (1:1) + benzoic acid; PG/VG (1:1) + benzoic acid + ncotin; PG/VG (1:1) + benzaldehyde; PG/GV (1:1)+ benzaldehyde + nicotine). Reported VOC: Benzene	Cartridge-based adsorption/ thermal desorption (ATD) followed by GC/MS Puff topography: 5s / 50 ml. Power: 6 ,13, 20 and 25W	Benzene was primarily measured in aerosols at high wattage with e-liquid containing benzaldehyde and benzoic acid.

Qu et al., 2019	Not reported	Three retail e-liquids and three lab made e-liquids composed of PG and VG at 3 different mixing ratios (7:3, 5:5, and 10:0) Reported VOC: Carbonyls (formaldehyde, acetaldehyde, acrolein, propionaldehyde and valeraldehyde, acetone, butyraldehyde, benzaldeyde, crotonaldehyde, isovaleraldehyde	HPLC/UV Puff topography: 2s Power: 3.6-7.0V	Emission factor (µg/puff) of various carbonyl compounds for FA (formaldehyde), AA (acetaldehyde), ACR (acrolein), and PA (Propionaldehyde). increased with increasing the voltage. from 3.6 to 7.0 V.
Salamancha et al., 2018	CE4 top coil atomizer (Central Vapors) with an Innokin iTaste VV V3.0 variable voltage battery	Halo Café Mocha (Nicopure Labs LLC). Reported VOC: Formaldehyde	HPLC Puff topography: 4s / 60ml Power: 4V, 7.3W	Comparison of aerosol formaldehyde levels with another study. Both used same e-cigarette, W, and e-liquid. The present study reported higher formaldehyde levels than the other and at levels estimated by the authors to result in exposure above OSHA workplace limits
Sleimann et al., 2016	eGo CE4, with a 2.6 Ω coil.	Classic tobacco, Apollo. PG:VG 50:50, nicotine 18 mg/mL. Reported VOC: 31 different substances, mainly various carbonyls, including, formaldehyde, acetaldehyde, acroleine. INicotine and nicotyrine.were also analysed.	Volatile carbonyls in aerosols were. determined using 2,4-dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges (Waters Corp., United States), extracted, and analyzed using HPLC with UV detection (Agilent 1200). Puff topography: 5s / 50 mL/s Power: 3.8V and 4.8V	The authors investigated the amount of carbonyls formed as a function of change in volt. Samples were retrieved both at the initial 5 first puffs and between the 30th to 40th puff, as the temperature of the aerosol increased until the temperature profile of the vapor leveled off around puff 30. The emission of carbonyls increased with increasing voltage concomitant with aerosol mass.
Son et al., 2020c	Refillable tank type e-cigarette with Nichrome dual-bottom coils with 0.8 Ω	100% VG, PG:VG 1:1 (v/v), and 100% PG. 12 mg/mL nicotine was added to all e-liquids Reported VOC: Formaldehyde and acetaldehyde, acetaldehyde, acrolein, propionaldehyde, crotonaldehyde, n-butylaldehyde, benzaldehyde, isovaleraldehyde, n-valeraldehyde, o-tolualdehyde and p-tolualdehyde.	HPLC-UV Puff topography: 3.8s / 90 ml Power: 6.4, 14.7 and 31.3 watt	Higher device power outputs increased formaldehyde emissions from all three base materials and acetaldehyde with PG:VG- and PG based e-liquids only. In addition, higher power output also generated other harmful carbonyls.
Stephens et al., 2019	KangerTech EVOD, bottom coil (1.8 Ω) KangerTech Subox Mini C (1.5 Ω), SSOCC atomizer	Propylene glycol (PG), glycerol (G), and Milli-Q water (70:20:10) Reported VOC: Formaldehyde, acetaldehyde, acetone, propionaldehyde, valeraldehyde.	Aerosols were collected by quartz fiber trapping. Carbonyls were analyzed by LC- diode array detector and confirmed by LC/MS. Puff topography: 4s / 55 ml. Power: 19, 13, 15, 30, 50W	From the Subox device there was an increase in carbonyl emission with increasing wattage, but this device appeared to emitt less carbonyls at same wattage compared to EVOD
Talih et al., 2017b	Four SOD coil head models (TFQ4, V8-Q4, V8-T8, and V8-T10; SMOK TFV series) and a Vapor Fi Platinum (VF) ECIG	50/50 (vol/vol) mixture of PG/VG Reported VOC: Formaldehyde, acetaldehyde, acetone , acrolein, propionaldehyde, benzaldehyde, valeraldehyde, p-tolualdehyde, hexaldehyde, glyoxal, methyl glyoxal	Aerosols sampled for VA species using DNPH-coated silica cartridges analyze by HPLC-UV Puff topography: 4sm 1L/min Power: 50, 75, 100W (SOD), 4 and 11W (VF)	There was a correlation between carbonyl emission and the ratio between wattage and surface area of the coil.
Talih et al., 2021	TF-N2 SMOK device, with 0.22 Ω coil	100% PG Reported VOC: Sum carbonyls: formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, benzaldehyde, valeraldehyde	Aerosol flow was drawn through a 47 mm glass fiber filter trap, followed by a DNPH-coated silica cartridge, analyzed by HPLC-UV Puff topography: 4sm 1L/min Power: 15-80W	The effect of power on carbonyl emissions was assessed and increased emissions as a function of wattage were observed
Talih et al., 2020b	SMOK®TF-N2 Air Core (0.12Ω), VaporFi Platinum™ (VF) (above-Ohm, 2.2Ω), and SMOK® V12-Q4 (sub-Ohm, 0.15Ω)	100% PG or 100% VG Reported VOC: Sum carbonyls: formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, benzaldehyde, valeraldehyde	Aerosol flow was drawn through a 47 mm glass fiber filter trap, followed by a DNPH-coated silica cartridge, analyzed by HPLC-UV Puff topography: 4sm 1L/min Power: TFN, 15-130W; V12-Q4, 50-180W; VF1, 1-20W	Higher coil temperature led to an increased carbonyl emission. The large variation in coil temperature was attributed to manufacturing variations
Talih et al., 2023	Kanger Subox Mini-C END with SSOC nichrome 0.5 Ω coil.	30/70 mix of PG/VG Reported VOC: Sum carbonyls: formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, benzaldehyde, valeraldehyde, hexaldehyde, glyoxal, and methyl glyoxal	Aerosol flow was drawn through a 47 mm glass fiber filter trap, followed by a DNPH-coated silica cartridge, analyzed by HPLC-UV Puff topography: 4s 8L/min Power: 30W	It was observed that higher coil temperature led to increased carbonyl emission. The large variation in coil temperature (100-500 ⌧) was attributed to manufacturing variations

Uchiyama et al., 2020	Three brands, variable wattage.	E-liquid consisting of PG (30%), and VG, (70%), nicotine (0.3%), menthol, and apple flavor. Reported VOC: Formaldehyde, acetaldehyde, acrolein, glyoxal, methylglyoxal, acetol, propylene oxide, glycidol	GC/MS, and LC photodiode array detector Puff topography: 3s /55 ml Power: 10-80W (250-550 ℃)	An increase in VOCs in the aerosol as a function of wattage was observed. The higher concentrations in one specific brand were attributed to higher temperature in the atomizer that reached more than 500 ℃.
Visser et al., 2021	JustFog Q16C clearomizers with 1.2 Ω and 1.6 Ω coils and eLeaf Pico batteries	Vanilla and mixed fruit liquids with PG/VG ratio of 70/30. Menthol liquid with propylene PG/VG ratio of 50/50. Fruit-flavored liquid had 3 mg/mL nicotine. Reported VOC: Lactaldehyde, formaldehyde, acetaldehyde, acrolein	Carbonyls in the emissions were trapped using a cartridge containing activated carbon and quartz fiber filters. The samples were analyzed with HPLC-DAD (diode array detection). Puff topography: 3s /55 ml Power: 10-25W	It was observed increased carbonyl emission with increasing wattage. Participants of the study correlated this with an increased sensitization of burned flavour.
Vreeke et al., 2018a	EC1: Innokin iTaste VV4 with Kanger EVOD clearomizer with MT32, 2.2 Ω single horizontal coil). EC2: Kanger Protank-2 clearomizer with MT32, 2.2 Ω single horizontal coil. EC3: Vaporfi Volt hybrid tank containing a 0.5 Ω single vertical coil.	1:1 ratio (by volume) of PG/VG Reported VOC: Dihydroxyacetone, a product that can be formed from glycerol.	The aerosol was passed through a dry cold trap, followed by an impinger of solvent, a 0.45 mm pore size syringe filter. Analyzed by H-NMR and confirmed by GC/MS Puff topography: 3s /55 ml Power: EC1, 6-15W; EC2, 5-15W; EC3, 20-40W.	An increased emission of dihydroxyacetone with increasing wattage from the e-cigs with horizontal coil was observed
Vreeke et al., 2018b	EC1. A SMOK Alien with a SMOK Baby containing a Q2 0.4 Ω single vertical coil. EC2: SMOK Alien with a Kanger Protank 2 Clearomizer containing a MT32 2.2 Ω single horizontal coil	PG/VG (1:1) and PG/VG (1:1) + 10% TA Reported VOC: Acrolein, formaldehyde, hemiacetals and acetaldehyde	The aerosol was passed through a dry cold trap, followed by an impinger of solvent, a 0.45 mm pore size syringe filter. Analyzed by H-NMR. Puff topography: 3s /55 ml Power: EC1, 55 and 66; EC2, 9 and 11W	It was observed that addition of triacetin to PG/VG increased emission of carbonyls with increasing wattage. The e-cig with horizontal coil had higher emissions of carbonyls than the e-cig with vertical coil

Table 16. Formaldehyde in aerosols as a function of changes in either watt, volt, or temperature (details on results)

Authors	**e-liquid**	**Volt/Watt/Ohm**	**Formaldehyde (µg/puff)**	**Mass vaped (mg/puff)**	**Formaldehyd pr mg mass vaped**
Dusautoir et al., 2021	PG <65%; G <35%; food flavourings; nicotine, 16 mg/mL	18 W 30 W	0.026 µg/p 0.065 µg/p	NR (Not Reported)	NA (Not Applicable)
El-Hellani et al., 2022	PG/G, of 30/70	30 W	0.229 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 1% sucralose	30 W 45 W	0.17 µg/p 18.7 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 3% sucralose	30 W 45 W	0.27 µg/p 225.5 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 5% sucralose	30 W 45 W	0.06 µg/p 287.9 µg/p	NR	NA
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.3 6.5 7.8 9.2	8.5 µg/p 21 µg/p 32 µg/p 51 µg/p	4.1 µg/p 6.2 µg/p 7.4 µg/p 7.1 µg/p	2.1 µg/mg 2.7 µg/mg 3.4 µg/mg 5.8 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.2 6.4 7.7 9.0	0.25 µg/p 1.5 µg/p 8.0 µg/p 17 µg/p	3.8 µg/p 5.4 µg/p 6.5 µg/p 7.7 µg/p	0.07 µg/mg 0.28 µg/mg 1.2 µg/mg 2.2 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.6 6.9 8.2 9.7	0.07 µg/p 0.07 µg/p 0.05 µg/p 0.59 µg/p	1.5 µg/p 3.9 µg/p 5.5 µg/p 6.9 µg/p	0.04 µg/mg 0.02 µg/mg 0.03 µg/mg 0.08 µg/mg

Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	7.3 8.9 11 13	0.13 µg/p 0.28 µg/p 0.14 µg/p 0.21 µg/p	2.3 µg/p 4.3 µg/p 6.7 µg/p 9.4 µg/p	0.06 µg/mg 0.06 µg/mg 0.02 µg/mg 0.02 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	10 15 20 25	0.13 µg/p 0.21 µg/p 0.31 µg/p 0.34 µg/p	7.5 µg/p 15 µg/p 22 µg/p 28 µg/p	0.017 µg/mg 0.014 µg/mg 0.014 µg/mg 0.012 µg/mg
Ogunwale et al., 2017	Halo Menthol Ice + 6 mg/ml nicotine	11.7 W. 4.2 V 14.7 W. 4.7 V 16.6 W. 5.0 V	13.0 µg/p 38.7 µg/p 82.0 µg/p	NR	NA
Qu et al., 2019 (ECB)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	11.7 µg/p 12.9 µg/p 13.2 µg/p 13.4 µg/p 13.6 µg/p 13.7 µg/p	8.8 mg/p 11.3 mg/p 11.3 mg/p 12.5 mg/p 11.7 mg/p 11.5 mg/p	1.33 µg/mg 1.14 µg/mg 1.17 µg/mg 1.07 µg/mg 1.16 µg/mg 1.19 µg/mg
Qu et al., 2019 (ECA)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	8.95 µg/p 9.34 µg/p 10.1 µg/p 10.1 µg/p 10.4 µg/p 10.6 µg/p	6.5 mg/p 7.7 mg/p 8.3 mg/p 8.2 mg/p 8.0 mg/p 8.0 mg/p	1.37 µg/mg 1.21 µg/mg 1.22 µg/mg 1.23 µg/mg 1.30 µg/mg 1.33 µg/mg
Qu et al., 2019 (ECM)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	9.75 µg/p 10.2 µg/p 10.4 µg/p 11.3 µg/p 11.5 µg/p 11.6 µg/p	6.5 mg/p 7.8 mg/p 9.1 mg/p 10.8 mg/p 10.7 mg/p 10.3 mg/p	1.50 µg/mg 1.30 µg/mg 1.14 µg/mg 1.04 µg/mg 1.07 µg/mg 1.13 µg/mg
Qu et al., 2019 (PV10)	PG (100%)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	2.23 µg/p 2.81 µg/p 3.05 µg/p 3.17 µg/p 3.30 µg/p 3.67 µg/p	14.2 mg/p 18.2 mg/p 15.7 mg/p 16.3 mg/p 16 mg/p 16.8 mg/p	0.16 µg/mg 0.15 µg/mg 0.19 µg/mg 0.19 µg/mg 0.21 µg/mg 0.22 µg/mg
Qu et al., 2019 (PV7)	PG/VG (70:30)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	9.58 µg/p 9.97 µg/p 9.97 µg/p 10.7 µg/p 10.7 µg/p 10.8 µg/p	5.5 mg/p 6.9 mg/p 7.6 mg/p 7.4 mg/p 7.4 mg/p 7.5 mg/p	1.74 µg/mg 1.44 µg/mg 1.31 µg/mg 1.45 µg/mg 1.45 µg/mg 1.44 µg/mg
Qu et al., 2019 (PV5)	PG/VG (50:50)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	7.05 µg/p 6.98 µg/p 7.09 µg/p 7.36 µg/p 7.49 µg/p 8.75 µg/p	6.5 mg/p 7.6 mg/p 8.2 mg/p 8.2 mg/p 7.9 mg/p 7.9 mg/p	1.08 µg/mg 0.92 µg/mg 0.86 µg/mg 0.90 µg/mg 0.95 µg/mg 1.11 µg/mg
Salamancha et al., 2018	Halo Café Mocha	7.3W	13.5 µg/p	6 mg/p	2.25 µg/mg
Sleiman et al., 2016	PG/VG (50/50)	3.3 V. 4.2 W 3.8 V. 5.5 W 4.3 V. 7.1 W 4.8 V. 8.9 W	53 µg/p 45.7 µg/p 35 µg/p 97 µg/p	NR	NA
Son et al., 2020 c	VG (100%)	6.4 W 14.7 W 31.3 W	0.90 µg/p (VG) 1.10 µg/p (VG) 1.26 µg/p (VG)	NR	NA

Son et al., 2020 c	PG/VG (50:50)	6.4 W 14.7 W 31.3 W	0.93 µg/p (PG:VG) 1.15 µg/p (PG:VG) 1.96 µg/p (PG:VG)	NR	NA
Son et al., 2020 c	PG (100%)	6.4 W 14.7 W 31.3 W	0.96 µg/p (PG) 1.20 µg/p (PG) 2.32 µg/p (PG)	NR	NA
Stephens et al., 2019	PG/G/Water (70:20:10)	10 W 15 W 30 W 50 W	0.18 µg/p 0.43 µg/p 3.38 µg/p 9.90 µg/p	5.32 mg/p 9.46 mg/p 23.6 mg/p 46.7 mg/p	0.034 µg/mg 0.045 µg/mg 0.14 µg/mg 0.21 µg/mg
Stephens et al., 2019		13 W 15 W	2.9 µg/p 4.1 µg/p	7.5 mg/p 5.7 mg/p	0.38 µg/mg 0.72 µg/mg
Talih et al., 2017b	PG/VG (50:50)	50 W 75 W 100 W	0.56 µg/p 0.97 µg/p 1.61 µg/p	27.8 mg/p 59.7 mg/p 104.2 mg/p	0.02 µg/mg 0.016 µg/mg 0.015 µg/mg
Talih et al., 2021	PG	15 W 31 W 50 W 60 W 70 W 80 W	0.037 µg/p 0.031 µg/p 0.11 µg/p 0.063 µg/p 0.082 µg/p 0.67 µg/p	3.1 mg/p 18.5 mg/p 30.9 mg/p 38.7 mg/p 42.0 mg/p 49.3 mg/p	0.01 µg/mg 0.0017 µg/mg 0.0036 µg/mg 0.0016 µg/mg 0.002 µg/mg 0.014 µg/mg
Talih et al., 2023	PG/VG (30:70)	30 W	0.015 µg/p (Low) 42.4 µg/p (High)	30.3 mg/p (low) 43 mg/p (high)	NA
Zhou et al., 2020.	PG/VG (70:30)	4 V 5 V	ND 0.42 µg/p	6.09 mg/p 14.31 mg/p	NA 0.029 µg/mg
Zhou et al., 2020.	PG/VG (70:30) + flavor + nicotine	4 V 5 V	ND 2.1µg/p	6.09 mg/p 14.31 mg/p	NA 0.15 µg/mg
Cancelada et al., (2021)a	VG/PG (65:35) with 6 mg/ml nicotine with 5 different coils, and 5 different puff topographies with 0.15 Ω M2 coil.	0.15 Ω (T8). 96.2 W 0.15 Ω (x4). 96.2 W 0.15 Ω (M2). 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.25 Ω. (M2) 57.8 W 0.6 Ω. (Q2) 24.1 W	0.35 µg/p 023 µg/p 1.0 µg/p 0.82 µg/p 0.31 µg/p 0.57 µg/p 0.49 µg/p 4.4 µg/p 0.12 µg/p	29.3 mg/p 43.7 mg/p 27.6 mg/p 45.6 mg/p 44.1 mg/p 45.7 mg/p 54.7 mg/p 20.8 mg/p 5.4 mg/p	0.012 µg/mg 0.005 µg/mg 0.036 µg/mg 0.018 µg/mg 0.007 µg/mg 0.012 µg/mg 0.009 µg/mg 0.21 µg/mg 0.022 µg/mg

a Cancelada et al.,(2021) investigated emission of VOC with same e-liquid, but with different coils and puff topography and was excluded as an eligible article included for VOC emission (Table 14) since it shows the effect of changing the coil with same resistance, but different geometry, and not specifically the effect of changing the watt for a specific design. In addition, the authors used 3 coils with different resistance and, thus different wattage as the same voltage was used. However, their results are included in Table 15, since it shows detailed information of emission of VOC and mass of vaped e-liquid with a sub-ohm E-cigarette device.

Table 17. Acetaldehyde in aerosol as a function of changes in either watt, volt, or temperature (details on results)

Authors	e-liquid	volt/watt/ohm	Acetaldehyde (µg/p)	Mass vaped (mg/p)	Acetaldehyde pr mg mass vaped
Dusautoir et al., 2021	PG <65%; G <35%; food flavourings; nicotine, 16 mg/mL	18 W 30 W	0.063 µg/p 0.161 µg/p	NR (Not Reported)	NA (Not Applicable)
El-Hellani et al., 2022	PG/G, of 30/70	30 W	7.56 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 1% sucralose	30 W 45 W	9.03 mg/p 50.4 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 3% sucralose	30 W 45 W	9.47 µg/p 297 µg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 5% sucralose	30 W 45 W	9.73 µg/p 34.7 µg/p	NR	NA
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.3 6.5 7.8 9.2	6.9 µg/p 17 µg/p 25 µg/p 41 µg/p	4.1 µg/p 6.2 µg/p 7.4 µg/p 7.1 µg/p	1.7 µg/mg 2.7 µg/mg 3.4 µg/mg 5.8 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.2 6.4 7.7 9.0	0.06 µg/p 0.33 µg/p 2.6 µg/p 8.3 µg/p	3.8 µg/p 5.4 µg/p 6.5 µg/p 7.7 µg/p	0.02 µg/mg 0.06 µg/mg 0.4 µg/mg 1.1 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.6 6.9 8.2 9.7	0.04 µg/p 0.06 µg/p 0.03 µg/p 0.53 µg/p	1.5 µg/p 3.9 µg/p 5.5 µg/p 6.9 µg/p	0.03 µg/mg 0.01 µg/mg 0.02 µg/mg 0.08 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	7.3 8.9 11 13	0.05 µg/p 0.06 µg/p 0.05 µg/p 0.06 µg/p	2.3 µg/p 4.3 µg/p 6.7 µg/p 9.4 µg/p	0.02 µg/mg 0.01 µg/mg 0.008 µg/mg 0.006 µg/mg
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	10 15 20 25	0.08 µg/p 0.16 µg/p 0.15 µg/p 0.16 µg/p	7.5 µg/p 15 µg/p 22 µg/p 28 µg/p	0.011 µg/mg 0.01 µg/mg 0.007 µg/mg 0.006 µg/mg
Ogunwale et al., 2017	Halo Menthol Ice + 6 mg/ml nicotine	11.7 W. 4.2 V 14.7 W. 4.7 V 16.6 W. 5.0 V	2.27 µg/p 13.4 µg/p 53.2 µg/p	NR	NA
Qu et al., 2019 (ECB)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	6.23 µg/p 6.51 µg/p 8.05 µg/p 9.20 µg/p 9.94 µg/p 10.8 µg/p	8.8 mg/p 11.3 mg/p 11.3 mg/p 12.5 mg/p 11.7 mg/p 11.5 mg/p	0.708 µg/mg 0.576 µg/mg 0.712 µg/mg 0.736 µg/mg 0.850 µg/mg 0.939 µg/mg
Qu et al., 2019 (ECA)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	2.40 µg/p 2.87 µg/p 3.03 µg/p 3.19 µg/p 3.59 µg/p 4.10 µg/p	6.5 mg/p 7.7 mg/p 8.3 mg/p 8.2 mg/p 8.0 mg/p 8.0 mg/p	0.369 µg/mg 0.373 µg/mg 0.365 µg/mg 0.389 µg/mg 0.449 µg/mg 0.513 µg/mg
Qu et al., 2019 (ECM)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	2.57 µg/p 2.77 µg/p 3.03 µg/p 3.81 µg/p 3.99 µg/p 5.20 µg/p	6.5 mg/p 7.8 mg/p 9.1 mg/p 10.8 mg/p 10.7 mg/p 10.3 mg/p	0.395 µg/mg 0.355 µg/mg 0.333 µg/mg 0.353 µg/mg 0.373 µg/mg 0.505 µg/mg

Qu et al., 2019 (PV10)	PG (100%)	3.6 V	1.28 µg/p	14.2 mg/p	0.090 µg/mg
		4.0 V	1.46 µg/p	18.2 mg/p	0.080 µg/mg
		4.5 V	1.46 µg/p	15.7 mg/p	0.093 µg/mg
		5.0 V	1.58 µg/p	16.3 mg/p	0.097 µg/mg
		6.0 V	1.73 µg/p	16 mg/p	0.108 µg/mg
		7.0 V	1.72 µg/p	16.8 mg/p	0.102 µg/mg
Qu et al., 2019 (PV7)	PG/VG (70:30)	3.6 V	1.01 µg/p	5.5 mg/p	0.184 µg/mg
		4.0 V	1.06 µg/p	6.9 mg/p	0.154 µg/mg
		4.5 V	1.24 µg/p	7.6 mg/p	0.163 µg/mg
		5.0 V	1.69 µg/p	7.4 mg/p	0.228 µg/mg
		6.0 V	1.73 µg/p	7.4 mg/p	0.234 µg/mg
		7.0 V	1.70 µg/p	7.5 mg/p	0.227 µg/mg
Qu et al., 2019 (PV5)	PG/VG (50:50)	3.6 V	0.50 µg/p	6.5 mg/p	0.077 µg/mg
		4.0 V	0.54 µg/p	7.6 mg/p	0.071 µg/mg
		4.5 V	0.54 µg/p	8.2 mg/p	0.066 µg/mg
		5.0 V	0.62 µg/p	8.2 mg/p	0.076 µg/mg
		6.0 V	0.63 µg/p	7.9 mg/p	0.080 µg/mg
		7.0 V	0.67 µg/p	7.9 mg/p	0.085 µg/mg
Sleiman et al., 2016	PG/VG (50/50)	3.3 V. 4.2 W	10 µg/p	NR	NA
		3.8 V. 5.5 W	9.2 µg/p		
		4.3 V. 7.1 W	31.8 µg/p		
		4.8 V. 8.9 W	50 µg/p		
Son et al., 2020c	VG (100%)	6.4 W	0.092 µg/p	NR	NA
		14.7 W	0.078 µg/p		
		31.3 W	0.083 µg/p		
Son et al., 2020c	PG/VG (50:50)	6.4 W	0.117 µg/p	NR	NA
		14.7 W	0.534 µg/p		
		31.3 W	0.553 µg/p		
Son et al., 2020c	PG (100%)	6.4 W	0.362 µg/p	NR	NA
		14.7 W	1.09 µg/p		
		31.3 W	1.02 µg/p		
Stephens et al., 2019	PG/G/Water (70:20:10)	10 W	0.059 µg/p	5.32 mg/p	0.011 µg/mg
		15 W	0.131 µg/p	9.46 mg/p	0.014 µg/mg
		30 W	0.298 µg/p	23.6 mg/p	0.013 µg/mg
		50 W	0.791 µg/p	46.7 mg/p	0.017 µg/mg
Stephens et al., 2019		13 W	0.157 µg/p	7.5 mg/p	0.021 µg/mg
		15 W	0.124 µg/p	5.7 mg/p	0.022 µg/mg
Talih et al., 2017b	PG/VG (50:50)	50 W	1.26 µg/p	27.8 mg/p	0.045 µg/mg
		75 W	1.38 µg/p	59.7 mg/p	0.023 µg/mg
		100 W	1.67 µg/p	104.2 mg/p	0.016 µg/mg
Talih et al., 2021	PG	15 W	0.43 µg/p	3.1 mg/p	0.14 µg/mg
		31 W	0.51 µg/p	18.5 mg/p	0.028 µg/mg
		50 W	0.10 µg/p	30.9 mg/p	0.003 µg/mg
		60 W	3.26 µg/p	38.7 mg/p	0.084 µg/mg
		70 W	8.97 µg/p	42.0 mg/p	0.21 µg/mg
		80 W	20.3 µg/p	49.3 mg/p	0.41 µg/mg
Talih et al., 2023	PG/VG (30:70)	30 W	4.46 mg/p 40.3 mg/p	30.3 mg/p (low range) 43 mg/p (high range)	NA
Zhou et al., 2020.	PG/VG (70:30)	4 V	ND	6.09 mg/p	NA
		5 V	0.16 µg/p	14.31 mg/p	0.011 µg/mg
Zhou et al., 2020.	PG/VG (70:30) + flavor + nicotine	4 V	0.069 µg/p	6.09 mg/p	0.005 µg/mg
		5 V	1.47 µg/p	14.31 mg/p	0.098 µg/mg

Cancelada et al., (2021)a	VG/PG (65:35) with 6 mg/ml nicotine with 5 different coils, and 5 different puff topographies with 0.15 Ω M2 coil.	0.15 Ω (T8). 96.2 W 0.15 Ω (x4). 96.2 W 0.15 Ω (M2). 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.25 Ω. (M2) 57.8 W 0.6 Ω. (Q2) 24.1 W	0.11 μg/p 0.09 μg/p 0.64 μg/p 0.42 μg/p 0.14 μg/p 0.12 μg/p 0.20 μg/p 2.0 μg/p 0.04 μg/p	29.3 mg/p 43.7 mg/p 27.6 mg/p 45.6 mg/p 44.1 mg/p 45.7 mg/p 54.7 mg/p 20.8 mg/p 5.4 mg/p	0.004 μg/mg 0.002 μg/mg 0.023 μg/mg 0.009 μg/mg 0.003 μg/mg 0.003 μg/mg 0.004 μg/mg 0.096 μg/mg 0.007 μg/mg

a Cancelada et al., investigated emission of VOC with same e-liquid, but with different coils and puff topography and was excluded as an eligible article included for VOC emission (Table 14) since it shows the effect of changing the coil with same resistance, but different geometry, and not specifically the effect of changing the watt for a specific design. In addition, the authors used 3 coils with different resistance and, thus different wattage as the same voltage was used. However, their results are included in Table 15 and Fig 3, since it shows detailed information of emission of VOC and mass of vaped e-liquid with a sub-ohm E-cigarette device.

Table 18. Acroleine in aerosol as a function of changes in either watt, volt, or temperature (details on results)

Authors	e-liquid	volt/watt/ohm	Acrolein (μg/p)	Mass vaped (mg/p)	Acrolein pr mg mass vaped
El-Hellani et al., 2022	PG/G, of 30/70	30 W	0.039 μg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 1% sucralose	30 W 45 W	0.158 μg/p 0.428 μg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 3% sucralose	30 W 45 W	0.095 μg/p 2.21 μg/p	NR	NA
El-Hellani et al., 2022	PG/G, 30/70 + 5% sucralose	30 W 45 W	0.069 μg/p 0.696 μg/p	NR	NA
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.3 6.5 7.8 9.2	0.23 0.47 1.0 5.5	4.1 μg/p 6.2 μg/p 7.4 μg/p 7.1 μg/p	0.05 0.08 0.14 0.78
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.2 6.4 7.7 9.0	<0.02 0.11 0.70 2.0	3.8 μg/p 5.4 μg/p 6.5 μg/p 7.7 μg/p	<0.01 0.02 0.11 0.26
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	5.6 6.9 8.2 9.7	<0.02 <0.02 0.08 0.23	1.5 μg/p 3.9 μg/p 5.5 μg/p 6.9 μg/p	<0.02 <0.02 0.05 0.03
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	7.3 8.9 11 13	<0.02 <0.02 <0.02 <0.02	2.3 μg/p 4.3 μg/p 6.7 μg/p 9.4 μg/p	<0.01 <0.006 <0.004 <0.003
Gillman et al., 2016	48% (wt/wt) PG, 48% (wt/wt) VG, and 2% nicotine.	10 15 20 25	<0.02 <0.02 <0.02 <0.02	7.5 μg/p 15 μg/p 22 μg/p 28 μg/p	<0.003 <0.002 <0.002 <0.002
Ogunwale et al., 2017	Halo Menthol Ice + 6 mg/ml nicotine	11.7 W. 4.2 V 14.7 W. 4.7 V 16.6 W. 5.0 V	0.122 μg/p 0.318 μg/p 1.621 μg/p	NR	NA
Qu et al., 2019 (ECB)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	0.30 μg/p 0.35 μg/p 0.45 μg/p 0.48 μg/p 0.48 μg/p 0.50 μg/p	8.8 mg/p 11.3 mg/p 11.3 mg/p 12.5 mg/p 11.7 mg/p 11.5 mg/p	0.034 μg/mg 0.031 μg/mg 0.040 μg/mg 0.038 μg/mg 0.041 μg/mg 0.043 μg/mg

Qu et al., 2019 (ECA)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	1.07 μg/p 0.91 μg/p 1.37 μg/p 1.81 μg/p 1.78 μg/p 1.83 μg/p	6.5 mg/p 7.7 mg/p 8.3 mg/p 8.2 mg/p 8.0 mg/p 8.0 mg/p	0.165 μg/mg 0.118 μg/mg 0.165 μg/mg 0.221 μg/mg 0.223 μg/mg 0.229 μg/mg
Qu et al., 2019 (ECM)	NR	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	0.40 μg/p 0.42 μg/p 0.59 μg/p 0.53 μg/p 0.92 μg/p 1.47 μg/p	6.5 mg/p 7.8 mg/p 9.1 mg/p 10.8 mg/p 10.7 mg/p 10.3 mg/p	0.062 μg/mg 0.054 μg/mg 0.065 μg/mg 0.049 μg/mg 0.086 μg/mg 0.143 μg/mg
Qu et al., 2019 (PV10)	PG (100%)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	0.04 μg/p 0.04 μg/p 0.04 μg/p 0.05 μg/p 0.05 μg/p 0.05 μg/p	14.2 mg/p 18.2 mg/p 15.7 mg/p 16.3 mg/p 16 mg/p 16.8 mg/p	0.003 μg/mg 0.002 μg/mg 0.003 μg/mg 0.003 μg/mg 0.003 μg/mg 0.003 μg/m
Qu et al., 2019 (PV7)	PG/VG (70:30)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	13.2 μg/p 1.55 μg/p 1.49 μg/p 1.69 μg/p 1.73 μg/p 1.70 μg/p	5.5 mg/p 6.9 mg/p 7.6 mg/p 7.4 mg/p 7.4 mg/p 7.5 mg/p	2.4 μg/mg 0.225 μg/mg 0.196 μg/mg 0.228 μg/mg 0.234 μg/mg 0.227 μg/mg
Qu et al., 2019 (PV5)	PG/VG (50:50)	3.6 V 4.0 V 4.5 V 5.0 V 6.0 V 7.0 V	0.07 μg/p 0.09 μg/p 0.15 μg/p 0.15 μg/p 0.19 μg/p 0.18 μg/p	6.5 mg/p 7.6 mg/p 8.2 mg/p 8.2 mg/p 7.9 mg/p 7.9 mg/p	0.011 μg/mg 0.012 μg/mg 0.018 μg/mg 0.018 μg/mg 0.024 μg/mg 0.023 μg/mg
Sleiman et al., 2016	PG/VG (50/50)	3.3 V. 4.2 W 3.8 V. 5.5 W 4.3 V. 7.1 W 4.8 V. 8.9 W	3 μg/p 8.5 μg/p 15.8 μg/p 21.5	NR	NA
Son et al., 2020c	VG (100%)	6.4 W 14.7 W 31.3 W	< 0.0004 μg/p < 0.0004 μg/p 0.252 μg/p	NR	NA
Son et al., 2020c	PG/VG (50:50)	6.4 W 14.7 W 31.3 W	0.043 μg/p 0.029 μg/p 0.199 μg/p	NR	NA
Son et al., 2020c	PG (100%)	6.4 W 14.7 W 31.3 W	0.067 μg/p 0.098 μg/p 0.209 μg/p	NR	NA
Talih et al., 2017b	PG/VG (50:50)	50 W 75 W 100 W	ND (Not detected)	27.8 mg/p 59.7 mg/p 104.2 mg/p	NA
Talih et al., 2021	PG	15 W 31 W 50 W 60 W 70 W 80 W	ND	3.1 mg/p 18.5 mg/p 30.9 mg/p 38.7 mg/p 42.0 mg/p 49.3 mg/p	NA
Talih et al., 2023	PG/VG (30:70)	30 W	ND (low range) 6.51 μg/p (high range)	30.3 mg/p (low range) 43 mg/p (high range)	NA
Zhou et al., 2020.	PG/VG (70:30)	4 V 5 V	ND 0.046 μg/p	6.09 mg/p 14.31 mg/p	NA 0.003 μg/mg

Zhou et al., 2020.	PG/VG (70:30) + flavor + nicotine	4 V 5 V	0.03 µg/p 0.52 µg/p	6.09 mg/p 14.31 mg/p	0.005 µg/mg 0.036 µg/mg
Cancelada et al., (2021)a	VG/PG (65:35) with 6 mg/ml nicotine with 5 different coils, and 5 different puff topographies with 0.15 Ω M2 coil.	0.15 Ω (T8). 96.2 W 0.15 Ω (x4). 96.2 W 0.15 Ω (M2). 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.15 Ω. (M2) 96.2 W 0.25 Ω. (M2) 57.8 W 0.6 Ω. (Q2) 24.1 W	0.07 µg/p 0.03 µg/p 0.07 µg/p 0.07 µg/p 0.03 µg/p 0.04 µg/p 0.05 µg/p 0.4 µg/p 0.01 µg/p	29.3 mg/p 43.7 mg/p 27.6 mg/p 45.6 mg/p 44.1 mg/p 45.7 mg/p 54.7 mg/p 20.8 mg/p 5.4 mg/p	0.002 µg/mg 0.0007 µg/mg 0.003 µg/mg 0.002 µg/mg 0.0007 µg/mg 0.0009 µg/mg 0.0009 µg/mg 0.019 µg/mg 0.002 µg/mg

a Cancelada et al., investigated emission of VOC with same e-liquid, but with different coils and puff topography and was excluded as an eligible article included for VOC emission (Table 14) since it shows the effect of changing the coil with same resistance, but different geometry, and not specifically the effect of changing the watt for a specific design. In addition, the authors used 3 coils with different resistance and, thus different wattage as the same voltage was used. However, their results are included in Table 15 and Fig 3, since it shows detailed information of emission of VOC and mass of vaped e-liquid with a sub-ohm E-c igarette device.

Table 19. VOC emissions in relation to other properties than changes in watt

Study	**Type of e-cigarette**	**E-liquid and substances analyzed**	**Method**	**Properties investigated and results**
Cancelada et al., 2021	SMOK Stick V8 kit with V8 Baby-M2 Core 0.15 Ω dual coil	Naked100 Euro Gold tobacco (USA vape lab). 35%, 65 % PG/VG, nicotine 6 mg/mL. Reported substances: Volatile aldehydes. formaldehyde, acetaldehyde, acrolein, acetone, propanal, crotonaldehyde, methacrolein, butanal, 2-butanone, benzaldehyde, valeraldehyde, m-tolualdehyde and hexaldehyde	2,4-dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges were used to collect volatile carbonyls, Analyzed by LC/UV-detection. Puff topography: 4s /50-500 ml Power: 3.8V	Air hole opening on VOC formation: Results shown for formaldehyde (50 ml puff volume). The authors reported a decrease in formaldehyde concentrations in the aerosol with an increase in air hole opening, keeping the puff volume constant. Air hole opening (%), formaldehyde (ng/mg) 0%, 48 ng/ml 25%, 39 ng/ml 50%, 32 ng/ml 100%, 18 ng/ml
Goto et al., 2022	Joyetech eVic-VTC Mini 75 W with 0.15 Ω coil, recommended range of W: 60–80: (GEEKVAPE)	Lab made: 50:50, PG/VG Substances analyzed: Formaldehyde and acetaldehyde	Formaldehyde measured with an inline electrochemical sensor (CO calibration, range of 50 ppm, MultiRAE Pro, RAE Systems, San Jose, CA). Acetaldehyde were measured with an inline photoionization detector (isobutylene calibration, range of 100 ppm, ToxiRAE Pro PID, RAE Systems, San Jose, CA). Puff topography: 2p/min, 100ml/p Power: 3.8V	Coil aging (number of puffs) on VOC formation: Formaldehyde and acetaldehyde (ppm): 0 puffs, 0.59 ppm, 12.68 ppm 840 puffs, 0.54 ppm, 17.03 ppm 960 puffs, 1.23 ppm, 20.35 ppm 1800 puffs, 625.17 ppm, 2845.33 ppm
Sleiman et al., 2016	eGo CE4, 4.8 V, 1 coil at 2.6 Ω	Classic tobacco, Apollo. PG:VG 50:50, nicotine 18 mg/mL	Volatile carbonyls in aerosols weredetermined using 2,4-dinitrophenylhydrazine (DNPH)-impregnated silica gel cartridges (Waters Corp., United States), extracted, and analyzed using HPLC with UV detection (Agilent 1200). Puff topography: 5s / 50 ml	Coil aging (number of puffs) on VOC formation: A single e-cigarette were used consecutively for nine cycles of 50 puffs- The authors reported that total aldehyde production increased by more than 60 %, while the temperature was measured to be constant.

Talih et al., 2016	NHALER 510 Atomizer with 2.5 Ω coil, powered by an eGo-T battery (3.4V, Joyetech)	Commercial: Liquid Express, Watermelon Chill, nicotine, 0 or 18 mg/mL (Liquid express) Reported substances: Formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde; crotonaldehyde, methacrolein, butyraldehyde, valeraldehyde	The aerosol was drawn from the mouth end of the DDA, through a glass fiber filter followed by a DNPH coated silica cartridge. Carbonyl analysis was performed by GC/MS Puff topography: 8s, 19.1 ml/s. Power: 100-350 ℃	Interdrip intervals on VOC formation: Formaldehyde and acetaldehyde (µg) for 15 puffs: 2 puffs interdrip interval, 19.7 µg, 269.35 µg 3 puffs interdrip interval, 71.30 µg, 822.70 µg 4 puffs interdrip interval, 88.06 µg, 1172.23 µg Increased emissions of carbonyls as a function of coil temperature and number of puffs were observed. This could be attributed to dry puffing where the liquid film around the coil was not maintained.

Table 20. ROS formation in e-liquid as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Bitzer et al., 2018a	Wismec Reuleaux RX200S Mod with 0.15 Ω Ni200 and 0.5 Ω SS316 coils (Uwell Crown).	PG/GLY: 0/100, 75/25, 50/50, 25/50, 100/0.	ERP spin trap and lipid peroxidation (MDA-eq) Puff topography: 5s, 30s puff interval, 500 ml/min. Power: 10W, 25W, 50W	The authors reported higher formation of free radicals (75:25 PG/GLY solution) when increasing the temperatures from 100℃ to 200℃ and 300℃ and from 10 to 50W.
Haddad et al., 2018	Vapor Fi, single coil (Supra ohm) Smok TFV, V8T8, V8-Q4, V8-T10 and TG-Q4 in SOS (Sub ohm device; SOD)	50/50 PG/VG solution with 12 mg/mL of nicotine	ROS measured by DCFH. Puff topography: 4s / 67 mL, 10s puff interval. Power: 1: 5Wand 11W 2: 50 - 200W	ROS flux nmol/s (per puff and per ml) Supra-ohm device: Single coil. 5 W: 0.238 ± 0.253 nmol/s (0.95 nmol/puff; 0.014 nmol/ml) 11W: 0.696 ± 0.096 (2.78 nmol/puff; 0.041 nmol/ml) Sub-ohm device: single coil (V8-T8) 50W: 0.114 ± 0.034 (0.46 nmol/puff; 0.007 nmol/ml) 75W: 0.109 ± 0.042 (0.44 nmol/puff; 0.015 nmol/ml) 100W: 0.167 ± 0.117 (0.67nmol/puff; 0.01 nmol/ml) 150W: 0.241 ± 0.029 (0.86 nmol/puff; 0.013 nmol/ml) 200W: 1.143 ± 0.606 (4.57 nmol/puff; 0.067 nmol/ml)
Son et al., 2019	Refillable tank type (The Council of Vapor, Walnut, Ca, USA). Batteries either Apollo Valiant or d-Sigelei-100W to provide heating range from 3-100W. Nichrome heating coil head dual bottom coil with 0.8 Ω resistance	Base material of either VG, PG:VG or VG with nicotine 12 mg/ml added. No flavor	*OH, measured as 2-OHTA Puff topography: 3.8s / 90 mL, 24s puff interval. Power: 6.4W, 31.3W	Changing the power output from 6.4 W to 31.3 W increased the formation of hydroxyl radicals (*OH) in the e-vapor. The authors did not report exact radical levels. Depending on base material (VG; VG:PG or PG), the highest power output formed respectively 5.8, 2.7 and 2.3 times more *OH compared with the lowest power output.

Zhao et al, 2018b	Brand A and B. No further information on type	Nicotine 10 mg/ml. Two flavors, tobacco and fruit.	H2O2 and total ROS, measured by Trolox method. Puff topography: 4s / 55 mL, 30s puff interval. Power: 3.7 V, 4.8 V, 5.7 V	Voltage dependent increase in ROS concentration (H2O2 and other ROS) per puff was observed for the investigated voltages (3.7, 4.8 and 5.7V). ROS concentration increased eight times as the voltage increased from 3.7V to 5.7V, with the H2O2 amount and its relative percentage of the total ROS increased. Differences between brands were noted as the total ROS concentration was highest for brand B.

Table 21. ROS emissions in relation to other properties than changes in watt, volt or temperature

Study	Type of e-cigarette	E-liquid	Method	Results
Son et al., 2019	Refillable tank type (The Council of Vapor, Walnut, Ca, USA). Batteries either Apollo Valiant or d-Sigelei-100W to provide heating range from 3-100W. Nichrome heating coil head dual bottom coil with 0.8 Ω resistance	Base material of either VG, PG:VG or VG with nicotine 12 mg/ml added. No flavor	*OH, measured as 2-OHTA Puff topography: 3.8s / 90 mL, 24s puff interval. Power: 6.4W, 31.3W	Air hole opening and ROS formation: Numeric results were only reported for the VG based and the PG:VG based e-liquids, indicating an increase of approximately 14% and 119 % respectively when comparing an air hole diameter of 1 mm with that of 2 mm at the highest wattage (31.3 W). Taken together, the levels of hydroxyradicals may be affected by air hole diameter, e-liquid composition and wattage.

Table 22. Metals identified in aerosol as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid and metals	Method	Results
Kapiamba et al., 2022	VOPOO, mod type	No flavor, no nicotine (no additional information provided). Metals reported: Cr, Cu, Mn, Ni, Zn	Metals collected on the Teflon filter were digested in 70% nitric acid and analyzed by ICP-MS. Puff topography: 2s / 35 ml Power: 5-45W	Significant increase for Zn and Cr in the aerosol collected at 25 and 45 watt compared to that collected at 5 watt. No significant increase for the metal elemental concentration in aerosol was observed for the aerosol collected at 45 compared to the aerosol content at 25 watt. The authors reported no change in Cu in the aerosol as a function of watt.
Rastian et al., 2022	Vaporesso Revenger Mini with GT8 (Nichrome) coil. Temp set to 204 °C	Commercial presented as 70/30 % VG, PG. Metals reported: Cr, Ni, Cu and Pb	Aerosols collected in a glass impinger and metals analyzed by a graphite furnace atomic absorption spectrometer (GFAA). Puff topography: 3s / 1.1 L/min Power: 50-75W (constant temperature)	Differences in metal elements in the aerosol produced at different watts were repoted. The temperature was held constant at 204°C irrespective of watt used. No clear trend in relation to difference in watt and metal elements in the aerosol could be observed. The authors reported an increase in Ni and Pb with increasing power, while Cr levels in aerosol seemed to decrease when higher than 60 watt was used.

Zhao et al., 2019	Open Device 1: Istick 25 with 0.2 Ω coil (Kanthal) and SMOK with stainless steel coil (0.6 Ω)	Commercial (9 liquids, 3 flavors reported together. Metals reported: Al, As, Cd, Cr, Cu, Fe, Mn, Ni, Pb, Sb, Sn, U, W, Zn	Aerosol was directed into a series of tubing and collected in a 1.5 mL centrifuge tube. Metals analyzed by ICP-MS Puff topography: 4s / 1.1 L/min Power: 20-80W (Istick 25), 40-200W (SMOK)	For the Istick 25 device the metal element level increased in the aerosol for all elements except Al and U when the watt was increased from 20 to 40. Increasing the watt from 40 to 80 increased the content of Pb and Zinc, whereas reduced levels of Fe and Sn was reported. For the other e-cigarette a watt range from 40 to 200 was investigated. The authors observed an increase in Cr and Mn for aerosols produced at 120 watt compared to 40 watt, however an increase in watt from 120 to 200 decreased the levels of the same elements

Table 23. Metals in aersols as a function of changes in either watt, volt, or temperature (details of results)

Authors	Watt	Al	As	Cd	Cr	Cu	Fe	Mn	Ni	Pb	Sb	Sn	U	W	Zn
	µg/kg e-liquid aerosol														
Rastian et al., (2019)	50 60 70 75				47 74 35 7.9	18 31 39 27			397 711 850 1728	4.0 13.5 10.1 128					
Zhao et al., 2019	20 40 80	5.41 6.7 5.39	0.11 1.57 1.7	0.06 0.13 0.46	0.06 3.22 3.03	6.3 107 244	4.44 131 9.5	0.42 17.4 29.5	8 768 277	6.5 89.5 792	0.06 4.84 5.48	0.51 322 38	0.06 0.05 0.06	0.06 0.15 0.05	387 2536 5555
Zhao et al., 2019	40 120 200	10.7 17.9 34.7	1.67 1.51 7.76	0.83 0.28 1.98	0.56 39.4 2.90	868 1480 1936	3.57 200 3.50	9.42 96.1 15.9	863 2491 789	848 839 1079	5.15 3.9 13.2	36.2 51.3 111	0.05 0.05 0.04	0.04 0.05 0.05	2664 5784 6952

Table 24. Metal concentrations as a function of the number of puffs

Study	Type of e-cigarette	E-liquid and substances analyzed	Method	Properties investigated and results
Jeon et al., 2023	Juul	Juul Virginia tobacco 5%. Substances reported: Al, Cr, Cu, Rb, Ba, Pb, V, Fe, Mn, As, Co, Ni, Zn, Rb, Sr, Ag, Cd, Ti, U…	The emitted aerosol was collected in the 1800 cm fluorinated ethylene propylene (FEP) condensation tube. Metals were analyzed by ICP-MS. Puff topography: 3s / 55 ml Power: Not reported	Coil aging (number of puffs) on metal transfer to aerosol: Significant higher concentrations in the 101–150 puff fraction compared to the 1–50 for Al, Cr, Cu, Rb, Ba and Pb. Non-significant higher concentrations of V, Mn and As was reported. For Co, Ni, and Zn the levels were reported to be similar
Kapambia et al., 2022	VOPOO, mod type.	No flavor, no nicotine (no additional information provided). Substances reported: Cr, Cu, Mn, Ni, Zn	Metals collected on the Teflon filter were digested in 70% nitric acid and analyzed by ICP-MS. Puff topography: 2s / 35 ml Power: 25W	Coil aging (number of puffs) on metal transfer to aerosol: Number of puffs; Cr (ng); Cu (ng); Mn (ng): 0-400; 134.43; 31.97; 9.89 400-800; 142.4; 70.5; 26.31 800-1200; 227.99; 129.76; 33.91

Rastian et al., 2022	Vaporesso Revenger Mini with GT8 (Nichrome) coil. Temp set to set to 204 °C C	Commercial presented as 30:70, PG:VG Substances reported: Cr, Ni, Cu and Pb	Aerosols collected in a glass impinger and metals analyzed by a graphite furnace atomic absorption spectrometer (GFAA). Puff topography: 3s / 1.1 L/min Power: 50-75W (constant temperature)	Coil aging (number of puffs) on metal transfer to aerosol and tank: The authors collected samples for each 10 puffs from 0 to 40 puffs without replenishing the e-liquid in the tank. Metal content was measured in both tank e-liquid and in aerosol. The author observed that metal concentrations of Cr, Cu, Ni and Pb in both the tank e-liquid and in aerosol increased as a function of the number of puffs. Thus, metal may be transferred from the metal components of the e-cigarette to the e-liquid and become aerolized.
Williams et al., 2017	Square 82 (PHD Marketing, Inc, Pomona, CA) Luxury Lites (Luxury Lites, Waco, TX) V2 Cigs (VMR Products LLC, Miami, FL) BlueCig (Lorillard Inc, Greenboro, CA)	Various commercial liquids Substances reported: Multiple metals.	Aerosol swere puffed into a 500 mL round bottom flask submerged in an ice bath. Metals analyzed by ICP-OES Puff topography: 4.3s / the lowest air flow that resulted in a robust aerosol formation Power: Not reported	Coil aging (number of puffs) on metal transfer to aerosol: The authors collected the aerosol for the first 60 puffs, and then from the last 60 puffs e-cigarette brand; first 60puffs; last 60 puffs (µg/10p): Square 82: 3.904 µg/10p; 2.553 µg/10p Luxury Lites: 2.583 µg/10p; 3.816 µg/10p V2 Cigs: 1.866 µg/10p; 2.720 µg/10p BlueCig: 1.302 µg/10p; 0.950 µg/10p The authors reported high variability for the elements in the aerosol at the first 60 puffs and for the last 60 puffs for the different brands investigated. Silicon was the dominant element identified in the aerosol both for the first and last 60 puffs

Table 25. Other substances in e-liquid aerosol as a function of changes in either watt, volt, or temperature

Study	Type of e-cigarette	E-liquid and PAH analyzed	Method	Results
Dusautoir et al., 2021	Third generation ModBox model, from NHOSS with 0.5 Ω kanthal coil	Propylene glycol <65%; glycerol <35%; food flavourings; nicotine 16 mg/mL Substances analyzed: Naphthalene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo(c) phenanthrene, benzo(a) anthracene, chrysene 5-methylchrysene, benzo(e)pyrene, benzo(b) fluoranthene, benzo(k) fluoranthene, benzo(a) pyrene, dibenzo(a,l)pyrene, dibenzo(a,h)anthracene, benzo(g,h,i)perylene, indeno(1,2,3-c,d)pyrene, dibenzo(a,e)pyrene, anthanthrene, coronene, cyclopenta(c,d)pyrene	HPLC coupled with a multi-wavelength fluorescence detector. Puff topography: 2s / 55ml Power: 18W, 30W	The sum of total PAHs measured was calculated for each e-cigarette aerosol. No significant difference in PAH content between Mb18W and Mb30W was reported. The following 5 out of 23 PAHs reported were detected in highest levels in the two aerosols (in pg/puff). Mb 18 (pg/puff) Naphthalene: 75.9 ± 9.5 Fluorene: 6.7 ± 1.5 Phenanthrene: 25.2 ± 8.2 Fluoranthene: 20.1 ± 11.8 Pyrene: 30.9 ± 9.2 Total PAHs: 183 ± 29 Mb 30 (pg/puff) Naphthalene: 92.2 ± 6.2 Fluorene: 5.0 ± 1.3 Phenanthrene: 22.8 ± 3.5 Fluoranthene: 11.5 ± 11.8 Pyrene: 30.9 ± 10.9 Total PAHs: 202 ± 57.

Table 26. Carbon monoxide levels as a function of changes in watt or volt

Study	Type of e-cigarette	E-liquid	Method	Results
Casebolt et al., 2019	Wismec Reuleaux RX2 20700 200W TC, with Efest 18 650 IMR 2500 mAh 35 A 3.7 V LiMN Batteries with 0.2 Ω stainless steel coil	Commercial: 2 different liquids, both 50:50 PG:VG with different flavor (Black Ice Flavoring or Strawnana)	Diode laser absorption spectroscopy. Puff topography: 4s / - Power:20-200 W	Increased CO measured with increasing watt applied. Higher CO concentrations measured from the Black Ice flavoring (approximately 150 ppm at 160 watt) than Strawnana (approximately 80 ppm at 160 watt). Results presented graphically.
El-Hellani et al., 2019	VGOD ProDrip dual-coil sub-ohm powered with a Lavabox battery. Coils (Kanthal) were manually built	Lab made: 30:70, PG:VG	FTIR, Avatar 360, equipped with a long path gas cell Puff topography: 3s / 16.67 mL/s Power:50-200 W	The authors observed no gaseous degradation products when under 100 W was used. At higher watt applied, a linear increase was observed. In addition, an increase in methane, ethylene and acetylene as a function of watt (graphically results) 125 watt, 42 mg/m3 CO 200 watt, 2060 mg/m3 CO.
Marocco et al., 2022	KangerTech refillable cartridges T3S series clear cartomizer (Rock Bottom Vapes, LLC, Longwood, Florida) with 1.8 Ω coil	Lab made: 1:48 % PG 50 % VG and 2 % nicotine 2: 45 % PG, 50 % VG and 5 % nicotine 3: 43% PG, 50% VG, 5% Nicotine, 2% Menthol	Q-Trak Indoor Air Quality (IAQ) Monitor (Model 8551, TSI Inc.) Puff topography: 4s / 55 mL/s Power: 3.7V, 7.6 W 5V, 13.9 W	CO did not reach detectable levels. CO2 levels were approximately 900 ppm at both voltages and e-liquid combinations investigated.
Son et al., 2020a	ReuLeaux RX200 (WISMEC Electronics, Guangdong, China) with an Aspire Cleito atomizer (Shenzhen Eigate Technology, Shenzhen, China) with 0.4 Ω Kanthal coil	Commercial: 1: Strawberry-watermelon, 3 mg/mL nicotine 2: Unflavored, no-nicotine	Model 8830 CO Analyzer (Teledyne Monitor Labs, Englewood, CO, USA Puff topography: 4s / 40 mL/s Power: 40, 50 and 60W	CO increased with increasing watt applied for both e-liquids investigated. For the flavored e-liquid by 0.057 µg/puff/W and 0.014 µg/puff/W unflavored e-liquid.

Table 27. Degradation products of sucralose as a function of changes in watt

Study	Type of e-cigarette	E-liquid	Method	Results
Moser et al, 2019	Crown IV Kit; Uwell with 0.2 Ω coil.	Labmade 30:70, PG:VG, with either 1 % or 7 % sucralose, and two commercial e-liquids containing sucralose according to ingredients list.. Chloropropanols investigated: Chloroacetaldehyde (CA), 1-chloro-2- propanol (1C2P), 2-chloro-1-propanol (2C1P), 1,3-dichloro-2-propanol (13DC2P), 2,3-dichloro-1-propanol (23DC1P), 3-chloropropane- 1,2-diol (3CP12D).	Gas chromatography (7890B, Agilent Technologies) equipped with a flame ionization detector (FID) and a mass spectrometer (MS) Puff topography: 3s / 84 mL/s Power: 200°C to 300°C at 60 W, at 20 °C increments.	Varius chloropropanols were formed in lab made sucralose containing e-liquids. No marked changes were reported for the amount of chloroporpanols as a function of changes in temperature. No chloropropanols were identified in the collected aerosol from the two commercial e-liquids tested, that were marked to contain sucralose

Table 28. Impact of coil materials on emissions

Study	Type of e-cigarette	E-liquid and substances analyzed	Method	Properties investigated and results
El-Hellani et al., 2019	VGOD ProDrip dual-coil sub-ohm powered with a Lavabox battery. Coils (1: Nichrome, 2: Stainless steel, 3: Nickel, 4: Kanthal) were manually built	Lab made: 30/70 PG/VG solution Substance reported: CO	Spectra were recorded on an Avatar 360 Fourier transform infrared (FTIR) spectrophotometer. Puff topography: 3s/p Power: 125W	Properties of coil and coil design Formation of CO in the aerosol was dependent on coil material and coil design. Coil/gaugel diameter/surface area/ wraps/CO (mg/m3±SD)a Nichrome: 24 / 3mm / 417 mm2/ 10 / 76.7B ± 64.1 Stainless steel: 24 / 3mm / 417 mm2/ 10/ 429.7A,B ± 376.2 Nickel: 26 / 3mm / 417 mm2/ 13/ 943.7A ± 459.6 Kanthal: 24 / 3mm / 417 mm2/ 10/ 77.7B ± 145.4
Williams et al., 2015	Four brands of EC, with nickel chrome coils, but different thick wires (the wire connected to the coil for electricity). A: Copper coated with silver, B: Copper coated with silver, C: Copper coated with tin, mostly covered with plastic sheet, D: Copper coated with silver	E-liquid not reported? Substances reported: Multiple metals.	Aerosol were puffed into a 500 mL round bottom flask submerged in an ice bath. Metals analyzed by ICP-OES Puff topography: 4.3s/p Power: NR	Metal analysis in EC parts and in aerosols High concentrations of tin were detected in the aerosol when tin solder joints were friable. Tin coating on copper wires also contributed to tin in the aerosol.

aThose groups not sharing same capital letter were reported significantly different with a p-value < 0.05

Appendix V - Studies eligible for RoB assessment and number of included studies after the RoB assessment.

Emission	Number of studies identified in each category	Number of studies included for each category after ROB assessment
Properties related to changes in watt, volt, or ohm		
E-liquid consumption and particle size and distribution	35	27
Volatile organic compounds	39	27
Radical formation	5	5
Metals in aerosol	3	3
Polycyclic aromatic hydrocarbons	1	1
Nicotine	15	14
Other properties	8	8
Properties of the wick		
No studies identified	0	0
Impact of coil materials on emission		
Metals	2	1
Other (carbon monoxide)	1	1
Other properties not defined in protocol		
E-liquid consumption and particle size and distribution	7	5
Volatile organic compounds	4	4
metals	4	4
Radicals	1	1
Nicotine	1	1

Appendix VI - GRADE assessment of the studies that investigated e-liquid consumption as a function of wattage

Certainty assessment							Device property	Effect	Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	imprecision	Other considerations	Changes in watte		
9	Gravimetric analysis of e-liquid consumed	Probably low	Not seriousa	Not seriousb	Not seriousc	Dose response observed, increased watt, increase in e-liquid consumedd	Lowest watt reported: 5.2W Highest watt reported: 80W	There was observed a dose response (increase in watt, increased e-liquid consumption) for the individual studies	■■■■ Moderate

a Differences in mg/puff of e-liquid were observed at a specific watt between studies. This heterogeniety is explained by differences in e-liquid used and differences between e-cigarettes. However, all studies reported an increase in e-liquid consumed as a function of watt, therefore we did not downgrade for inconsistency.

b We evaluated indirectness not to be of concern since all studies used e-cigarettes and weigthed amount of e-liquid before and after use at the different wattages investigated.

c The studies reporting on e-liquid consumption showed differences in e-liquid consumption at similar watts likely associated with various e-cigarette and e-liquid combinations. However, we did not downgrade for imprecision as all studies showed an increase in e-liquid consumption with increasing watt.

d We upgraded our confidence by one level (low to moderate) due to the dose (watt) response (e-liquid consumption) observed.

e One study (Li et al., 2021) did not report specific watt in their study