Evidence From the Scientific Assessment of Electronic Cigarettes and Their Role in Tobacco Harm Reduction *

by

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SUMMARY

While smoking remains a main global cause of preventable morbidity and mortality, a potential inflection point has arrived where it could become possible for non-combustible nicotine products to displace cigarettes and reduce risk for smokers who transition completely from smoking. These have proven consumer satisfaction and are now widely and increasingly available globally. One of the most prominent of these nicotine products are electronic cigarettes (ECs), which are used daily by millions of current and former smokers. The category is not without controversy as these products are not risk free and can cause nicotine dependence. The differing interpretation of science assessing ECs has transpired into inconsistent regulation and product standards, providing an environment for its fragmented manufacturing base which allows for variable product quality and in turn, product quality variability has impacted on how they are viewed. In this review, we assess published scientific evidence to evaluate whether, on balance, ECs fulfil a tobacco harm reduction role by reducing health risks relative to smoking and providing a viable alternative for smokers while having limited appeal to non-smokers. [Contrib. Tob. Nicotine Res. 30 (2021) 63–108]

ZUSAMMENFASSUNG


RESUME

Sachant que le tabagisme demeure, au niveau mondial, une cause majeure de morbidité et de mortalité évitables, un point d’inflexion potentiel est atteint où il pourrait devenir possible pour des produits non combustibles contenant de la nicotine de supplanter la cigarette et de réduire le risque pour les fumeurs abandonnant complètement le tabac. Ces produits non combustibles apportent aux consommateurs

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1. INTRODUCTION

Smoking remains an important cause of preventable morbidity and mortality (1). The World Health Organization (WHO) currently estimates that worldwide, around 1.3 billion adults smoke (2). The overwhelming majority of the disease risk is acknowledged to come from compounds formed during combustion of tobacco at very high temperatures (~950 °C) (3, 4). Of roughly 6,500 compounds (5), about 150 are known toxicants (6) that contribute to smoking-related diseases, such as cardiovascular and respiratory diseases, and cancers. These toxicants also increase the risk of disability and death by other diseases; risks rising with increasing duration of regular smoking. However, excess risks are substantially reversible with smoking cessation (7). Nevertheless, not all nicotine users want to quit, and others find it difficult to do so.

In 2010, the WHO published its Framework Convention on Tobacco Control (FCTC) treaty (8), creating aspirational policy goals for the 181 member states that ratified it. Traditionally, WHO has taken an absolute tobacco control approach to smoking, despite article 1(d) in the FCTC advocating for harm reduction strategies. Since its publication, many countries have implemented the associated guidelines to varying degrees. Since these goals were published, various alternative nicotine products have become commercially available (e.g., electronic cigarettes (ECs), tobacco-free nicotine pouches, and other vapour products), which has led to increasing consideration of the concept of tobacco harm reduction. Harm reduction initiatives involving alternatives to smoking must aim to protect youth and non-smokers from uptake, including by regulating of products, advertising, promotion, and sponsorship (9). This principle involves reducing the risk to smokers by offering satisfactory alternative products with lower risk profiles (10-13). For example, in Sweden, where there is high prevalence of snus use, daily smoking prevalence is one of the lowest in Europe. Only 7% of the adult population were daily smokers in 2020 (14). Snus is less harmful to health than smoking (15), and Swedish men, who are the predominant snus users, have among the lowest rates of lung cancer incidence and tobacco-related mortality worldwide (16). The potential role of snus in a tobacco harm reduction strategy has been recognised by the US Food and Drug Administration (FDA), granting modified risk orders for eight snus products in 2019 (17, 18).

A widely available alternative nicotine product is ECs. Use of ECs is commonly known as vaping and users are known as vapers. These products heat a liquid (termed e-liquid) containing ingredients that function as carriers (e.g., propylene glycol (PG) and vegetable glycerin (VG)) and may contain flavours and/or nicotine. Compared with tobacco combustion, e-liquids are heated to only around 250 °C and release an aerosol that is much less complex than cigarette smoke, having substantially fewer and lower concentrations of compounds (19-22). Systematic reviews indicate substantially decreased disease risk compared with smoking through greatly reduced exposure to toxicants and carcinogens (23-28), although the risks are not wholly eliminated nor yet fully characterised. Several governments, including those in the UK (24, 29), Canada (30), and New Zealand (31) support use of ECs as reduced-risk alternatives to smoking.

Where manufacturing is actively regulated and monitoring systems are in place, EC quality tends to be high (32) and numbers of reported adverse and serious adverse events leading to morbidity or mortality are low (33). By contrast, if poorly made or illegal products are allowed to enter markets, they substantially increase the risks of adverse events. In the electronic vapour acute lung injury (EVALI) crisis in the USA in 2019, non-regulated e-liquid containing vitamin E acetate and medium-chain triglycerides that are often used in consumption of cannabis and tetrahydrocannabinol were illegally used as additives, causing severe lung injury in some users (34, 35). This tragedy killed 68 people and injured over 2,000.

This review paper considers the role of ECs in tobacco harm reduction. It provides a high-level account of the evolution of EC design, safety and performance, and methods of testing. Scientific evidence is assessed in relation to acute and long-term health risks associated with EC use. Finally, it discusses how ECs perceptions and use behaviours could impact a harm reduction strategy as well as how available evidence can be used to evaluate health outcomes at population level.

2. PRODUCT DESIGN AND REGULATION

2.1 EC design basics

ECs were introduced to the market in 2004 and came to prominence around 2010. Despite this short period, the types of devices have cycled through several generations (Figure 1) (28), in each of which many different devices are available (36). From simple closed, low-power ‘cig-a-like’ devices (generation one), they transformed to refillable long-term use (generation two) and modifiable (generation three) systems, and further to discreet closed system devices with many safety features and improved nicotine delivery (generation four; Figure 1).
The basic elements of ECs are a battery connected to a heating element and an e-liquid reservoir. In first generation, single-piece cig-a-like products, all parts are encased into one (usually disposable) unit. The three-piece open systems of generations two and three consist of a separate battery, e-liquid cartridge, and atomizer (vaporizes the e-liquid), and parts and components may be swapped to customize the vaping experience (e.g., by increasing voltage, tank size, and/or e-liquid strength and flavour). Fourth-generation two-piece products consist of a battery and a cartomizer (a combined e-liquid cartridge and atomizer), which is the only exchangeable part. EC emissions may differ by product characteristics and operation and user behaviour (28). Many manufacturers’ design changes have been based on feedback from users searching for products that can meet their nicotine preference with sufficient satisfaction to enable them to replace cigarettes while favoring safety and flexibility (21, 36). In most countries, cig-a-like devices account for only 15% of the EC market, except in the USA, where they are used by around 50% of vapers (37).

The most common reasons for smokers rejecting ECs relate to performance (mimicking smoking and effectiveness at lessening cravings for smoking), but other common reasons are ease of use. In a survey published by Action on Smoking and Health (ASH) (38), 7% of users stopped using ECs because of difficulties in replacing components, refilling e-liquid, or due to leaking. WADSWORTH et al. (39) found that the ease of using cig-a-like ECs (confidence in nicotine dose, no refilling required, ease of availability compared with later-generation devices, etc.) made them a popular first device for vapers. By contrast, third-generation modifiable models were considered “bulky” or “scary”. However, cig-a-likes (39) and e-cigarettes in general (40) were often found to be unsatisfactory.

An unpleasant problem is so-called dry wicking, more commonly known as “dry puff”, which is caused when the wick in the atomizer is not saturated, leading to the coil becoming overheated and thermal breakdown of solvents in e-liquid (41-47). The dry wick effect can occur when the e-liquid runs out and the user puffs deeply or if the voltage on modifiable devices is too high for the heating system. While this phenomenon is thought to increase the emission of toxicants (42), it causes a very unpleasant acrid taste (48) that is generally viewed as sufficiently arresting to prevent harm (24). In generation four products, some manufacturers have introduced pre-set power settings to help users to vary their vaping experience while avoiding dry wicking. For example, a distiller-plate heating system, which heats the e-liquid directly and replaces the coil and wick system, has increased nicotine delivery while minimizing the risk of dry puffs (21).

2.2 Use of flavours

Thousands of flavours are available for ECs, and even within individual flavours, many variations in formulations exist. Sensorial aspects, such as sweetness, coolness, and vapour visibility or smoothness, play important parts in product acceptability (49-51). A systematic review by ZARE et al. (52) found that all vapers preferred flavoured ECs, particularly sweet flavours, irrespective of age group. Adult consumers identify taste and variety of flavours as important characteristics of ECs (53). Most first-time purchases of ECs and e-liquids contain fruit flavours (54, 55). However, some studies suggest that flavours could be a determinant for adolescents trying ECs and, potentially, transitioning to smoking (56) or that flavours could reinforce the reward obtained from nicotine vaping products, increasing their potential for abuse liability (57, 58). An ASH survey (59) found that fruit flavours have overtaken both tobacco flavours and mint as the preferred e-liquid, accounting for nearly one-third of flavoured e-liquids used, and those using fruits or sweet flavours were more likely than tobacco flavour users to vape in order to quit smoking (60).
2.3 Product regulation

In many countries, ECs are regulated (in around 100 countries) (61), but the regulations are inconsistent and generally cover marketing, labelling, ingredients, and/or taxation, leading to highly variable product standards globally. However, only six countries have no regulations beyond minimum age for purchase (61). Marketing authorizations or product notifications/marketing applications may be required before products can enter the market. Premarket authorizations involve the regulator giving permission for marketing after review of an application, placing some of the responsibility for a product on the regulator. By contrast, with product notifications/marketing applications, while the regulator may act on information provided, responsibility for the product remains with the submitter.

The European Parliament, the US Food and Drug Administration (FDA), and various other national authorities request data on ingredients and various compounds in emissions, including types, quantities, and origins. Forty-two countries have banned ECs, most frequently based on the perceived risk of youth nicotine addiction or the potential that yet unknown long-term effects of vaping might outweigh any health benefits (61-64). In the USA, regulation of ECs was introduced in 2016 (65). All new tobacco products, including ECs despite their lack of tobacco leaves, are subject to approval via Pre-Market Tobacco Product Applications (PMTA) (66). Manufacturers that wish to be able to claim that an individual tobacco product (but not a product class) reduces risk to health compared with smoking must also make a Modified Risk Tobacco Product Application (67, 68). Each submission requires a dossier with description and formulation of the product, description of non-clinical and clinical research findings relating to the effects of the product on tobacco-related diseases and other health-related conditions, how it will be used, as well as, examples of labelling and a description of how the product would be marketed. So far, numerous Pre-Market Tobacco Product Applications have been made for ECs but no Modified Risk Tobacco Product Application submission for ECs has yet been approved by the FDA. Dossier review times are expected to run into several years, making it likely the market will not easily benefit from product improvements as the category develops.

In the EU, the Tobacco Products Directive 2014/40/EU (TPD2) regulates the manufacture, sale, and marketing of tobacco products (69). It incorporates a product notification system and aims “to facilitate the smooth functioning of the internal market for tobacco and related products, taking as a base a high level of health protection”. The first factor requires an assessment of the product relative to the products already on the market, whereas the second focuses on the safety of the product itself. The TPD2 sets certain minimum safety and quality requirements, including, but not limited to, maximum nicotine concentration (20 mg/mL) and maximum volumes for cartridges, tanks, and nicotine liquid containers (2 mL), child-resistant and tamper proof features on devices and e-liquid bottles, and refilling systems that prevent leaking. These are in addition to EU safety regulations on restriction of hazardous substances in electrical and electronic equipment products (70), the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation (71), testing requirements for electrical parts, and monitoring and reporting of adverse events (69). TPD2 is expected to be revised in the mid-2020s.

In most countries, advertising and marketing of ECs is highly controlled in terms of where and what information may be displayed and how. In the UK, the Committee of Advertising Practice does not allow advertising of ECs to make medicinal claims (e.g., can help with smoking cessation) unless they have marketing authorization from the Medicines and Healthcare Products Regulatory Agency, and messages must not appeal to youth or encourage non-smokers or non-nicotine-users to use ECs (72). In the US, modified risk claims can be made only for products authorized by the FDA via the Modified Risk Tobacco Product Application process (73). A few countries, like Canada and New Zealand, allow promotion of the use of ECs as less harmful alternatives to tobacco smoking by providing balanced risk information for consumers (74, 31). As well as top-line requirements, further detail on interpretation and compliance are provided by regulatory guidance documents, national, regional, and international technical product standards, and voluntary industry codes. Technical committees creating standardised safety and quality guidance for ECs have been set up at the International Organization for Standardization (ISO) and the European Committee for Standardization (CEN), involving experts from industry, regulators, consumers, and other relevant stakeholders. Each has published two technical standards on generating emissions for measurements, what to measure in emissions, device safety, and analytical methods for measuring the main components in e-liquids (75-78). Further guidelines are being developed on electrical safety, manufacturing, ingredients, additional emissions and e-liquid measurement methods, consumer information, and labelling. Adoption of product standards is important to consumers to inform them about the quality of ECs, and to regulators and industry to clarify methodologies and data generated for marketing applications. Specifically, a framework of testing standards for ECs has been proposed, as many methods used had simply been adapted from cigarette testing methods. This will enable clearer comparison of aerosol yields within and across different product categories, including cigarettes (79).

3. PRODUCT SAFETY AND STEWARDSHIP

When ECs were first introduced, concerns were expressed about e-liquid after the number of calls to poison centres reporting exposure and irritation of skin or eyes with contact rose (80-82), but the risk of incidents has been reduced by changes in product design and labelling, e.g., non-spill e-liquid cartridges in closed ECs, improved information for use of open, refillable ECs and measures to take when accidental spills do occur, and testing of appropriate concentration ranges for ingredients. Nevertheless, some of the measures that could increase the safety are, for example, by developing child-resistant mechanisms for puff-activated products. For open products, the tanks should be child resistant and refilling could be leak-free, such as with a dock-and-lock mechanism. Exploding devices and batteries occur infrequently but have
led to severe burns and projectile injuries. These events are generally related to use of inappropriate chargers not supplied with the product that deliver too much current to the battery, leading to thermal runaway and generation of flammable and explosive gases (83). Well-designed products should meet international standards for protection against overcharging (76) and ensure sufficient venting capacity of the battery compartment. Likewise, battery quality should comply with existing international standards. EC products in Europe are covered directly by Electromagnetic Compatibility (EMC) Directive (2014/30/EU) (84) and Restriction of the Use of Certain Hazardous Substances (RoHS) Directive (2011/65/EU) (85), as indicated by the CE marking. Additionally, aspects of the General Product Safety (GPS) Directive (2001/95/EC) apply (86). The GPS sets out safety requirements for all consumer products being placed on the European market (and allows the use of adjacent standards, such as within the low-voltage-device safety standards, to control failure modes and risks), but is not itself associated with CE marking. Occasionally, battery explosions have been caused by improper storage or modification by users (28), and this issue requires further user education.

The European Committee for Standardization provides practical and enforceable requirements related to electrical safety, leakage and breakage, child resistance and some high-level device material considerations (76). ECs continue to be a developing product category and best practice guidance will thus require regular updating. Product stewardship for ECs has been developed by several EC manufacturers to address materials and ingredients, interactions of the e-liquid and the device (e.g., aerosol laboratory and clinical testing), and post-marketing surveillance (e.g., customer feedback or complaints, product sustainability, etc.). A potential approach for toxicological stewardship of ECs is summarised in Panel 1 (87-89). The need for purity requirements and exclusion of ingredients with certain toxicological properties has gained widespread recognition (90). However, the basic principle that the dose determines the level of toxicological risk seems often to be forgotten, leading to purported adverse effects in the literature based on in vitro cytotoxicity or other effects without human exposure contextualisation. (91).

Panel 1. EC stewardship toxicological best practice.

- Nicotine and humectants should be of pharmaceutical grade purity
- Flavourings should be food grade purity
- Protect consumers from ingredients identified as carcinogens, mutagens, reprotoxics, and respiratory allergens
- Manufacturers should maintain an additional negative list of ingredients that have proven to be unsuitable for use in vaping products (e.g., diacetyl, vitamin E acetate, triglycerides) and follow regulatory guidance about any other substance
- Toxicological risk assessments should be performed for each e-liquid to demonstrate ingredients and concentrations in e-liquid are supportable
- Conduct chemical and toxicological assessments of aerosol for every device and e-liquid variant (can benefit from a bridging approach)

Besides addressing ingredient selection, an e-liquid toxicological risk assessment should determine whether the levels of the ingredients are suitable for the intended use (92, 93). In vitro assessments, such as cytotoxicity tests, and comparison to reference materials enable quantitative translation of effects to real-life situations. Additionally, a robust stewardship process should monitor consumer complaints and analyse them to ensure safety and engagement with the product continuous improvement process.

4. INVESTIGATION OF ACUTE AND LONG-TERM HEALTH RISKS

Multiple scientific frameworks for risk assessment have been presented that outline the approach for investigating the risk profile of non-combustible tobacco and nicotine products (13, 94-96). Broadly, all frameworks are underpinned by investigation of acute and long-term risk from using ECs in studies assessing chemistry, toxicology and clinical outcomes, and also by the perceptions and behaviours of users and non-users of ECs. In this section, we present published data from multi-disciplinary scientific studies of ECs generated within product assessment frameworks and investigating acute and long-term risks from using ECs.

4.1 Chemical and physical characterization

Compounds of interest in ECs have often been based on smoking toxicant emissions (97) and many studies use smoking as a comparator, meaning that smoke toxicants have been the focus of most assessments so far (98-102). Investigational approaches are, therefore, evolving in response to emerging evidence and growing understanding of EC aerosol composition. The EU TPD2 stipulates chemical emissions testing for multiple priority compounds, including acetaldehyde, acrolein, and formaldehyde (84). The US FDA has identified 92 harmful or potentially harmful constituents (HPHCs) in addition to nicotine (103) and public comment was recently sought on the proposal to add a further 19 compounds to the list (104). However, to our knowledge, only one study has investigated the emissions of these additional HPHCs (22). In practice, it has been suggested that Pre-Market Tobacco Product Applications should report at least 32 compounds (66). ECs generally do not reach temperatures higher than 250 °C during normal use or more than 350 °C under dry wicking conditions (105). However, a huge variety of devices and e-liquids exist (106) and many different puffing conditions and analytical techniques have been used to assess them (42, 107-109), but, overall, results indicate significantly lower levels of toxicants in EC aerosols than in cigarette smoke (20, 22, 43, 44, 102, 110, 111).

4.1.1 Methodological considerations in vaping products analytical testing

Despite the relative simplicity of EC aerosol, consideration must be given to aerosol collection methods and measurement of specific analytes. For example, a review of papers that measured carbonyl emissions from ECs showed many variations in the measurement techniques, including puffing
regime, aerosol collection, and analytical methodology, making data comparisons difficult (41, 42). Reducing variability would maximize sensitivity of reported values (43). The CORESTA Recommended Method No 81 (112) includes standardised puffing conditions for ECs that have now been used in multiple emissions testing studies (20-22, 113-115).

Potential contamination from the testing environment (e.g., the presence of volatile organic species in occupational and residential room air) is a well-documented phenomenon. Indoor air quality reference values have been established for several species (20). The presence of an analyte in a laboratory reagent used for testing, for example carbonyls in 2,4-dinitrophenylhydrazine, is also well recognized (43). Given the low levels of most compounds in EC emissions, use of air and blank controls and management of the chemical background of the testing environment are crucial to provide context (e.g., contribution of non-product-related compounds of interest) and minimize errors in the analytical data (20, 116). Reporting control data as standard will improve interpretability of results.

### 4.1.2 Sources of toxicants in e-liquids and aerosol

The number of components in e-liquids is estimated to be around 113 (28) compared with around 600 in tobacco cigarettes (109). In high-quality manufactured ECs, the main sources of toxicants in aerosol are attributed to impurities in liquid, degradation of the e-liquid ingredients, and device components. Most compounds associated with e-liquid formulation are either not detected or are very close to the limit of quantification (113, 117).

#### 4.1.2.1 Impurities and leaching

Carbonyl compound levels can increase with increasing flavour content. Retail flavours were added to a 1:1 PG-VG mixture at 5-50% (v/v) and carbonyl compound levels increased linearly by 1.3-10.5 times (118). However, these concentrations are not representative of commercial e-liquid formulations and were sampled in a non-standard puffing regime. In flavours derived from the extraction of cured tobacco leaf, major tobacco-derived toxicants (e.g., tobacco-specific nitrosamines and nitrates) were present at very low levels compared to those in tobacco products but whether these transferred to aerosol was not assessed (100).

E-liquid components can cause unintended formation of toxicants, such as acetoin leading to formation of diacetyl (119). Reduction of toxicants in e-liquid, directly or by avoiding reactions with other components, may be achieved with good stewardship during product development (87).

Metals in e-liquid are generally impurities or are leached from the cartomiser or device materials through contact (120-122), but this occurrence is generally restricted to earlier EC designs (123-126). A selection of results from studies investigating metals in different devices has been compiled in Table 1. In a study of 15 trace elements in 22 e-liquids from various markets, NA et al. (129) reported that levels of some metals increased and transferred to aerosol after e-liquid was in contact with coils and open-system atomizers for 7 days, but this circumstance would be unusual for most EC users. Ratios of metals before and after use differed, indicating transfer of metals into aerosol in six liquids (129). However, generally, heavy metals do not seem to transition to aerosol (44). BELUSHKIN et al. (116) found higher concentrations of heavy metals in aerosol than in air blanks in only two samples of e-liquid among a wide range of products from multiple manufacturers. Similarly, MARGHAM et al. (20), found that the measured metals in EC aerosol were not significantly different from those in air blanks. High-powered and open-system devices are likely to have higher metal content in aerosol than closed systems (130), but none of the metal content is likely to generate significant adverse health effects (131). FOWLES et al. (132) concluded in a review that metals in vapour could constitute a health risk to EC users but that high product standards can minimize exposure and reduced health risks associated with metals in EC aerosol.

#### 4.1.2.2 Thermal degradation

Aldehyde formation may be influenced by e-liquid ingredients, overheating and dry wicking (41-47) and e-liquid oxidation through direct contact with the nickel-chromium heater coil (133-134) are the dominant causes. Improved coil designs and wicking materials that enhance e-liquid flow to the heaters can reduce the risk of these phenomena (135-137). In fourth-generation ECs, the levels of the key carbonyls of concern – formaldehyde, acetaldehyde, and acrolein – are greatly reduced compared to those in cigarette smoke (22). Table 2 illustrates the complexity of comparisons due to the differences in methodological and reporting approaches.

Nicotine salts in e-liquids have lower volatility than freebase nicotine, enabling enhanced nicotine delivery without increased irritation during vaping (138). Pharmacokinetic assessments indicate that the concentration of nicotine delivered is close to that in cigarette smoke, and the efficiency of delivery is improved compared with e-liquids containing free-base nicotine (139-141). At least six different acids have been identified in e-liquid formulations, alone or in combination, but the most common are lactic, benzoic, and levulinic acids (142). Nicotine benzoate is one of the most thermally stable organic acids but can decarboxylate under high temperatures to form benzene or phenol (143). Only one study has shown such degradation in ECs, and this effect was limited to high-powered open systems (144).

#### 4.1.3 Second-hand exposure to vaping aerosol

Harmful health effects from secondhand smoke exposure have been widely reported (145). Although EC aerosol is much simpler than cigarette smoke and does not generate sidestream smoke, bystanders are still exposed to exhaled compounds, especially in indoor conditions.
Table 1. Comparison of metal levels in e-cigarette vapour versus cigarette smoke from published studies analysed.

<table>
<thead>
<tr>
<th>Category</th>
<th>Device/Cigarette</th>
<th>Regime</th>
<th>No. of puffs</th>
<th>Mercury</th>
<th>Cadmium</th>
<th>Lead</th>
<th>Chromium</th>
<th>Nickel</th>
<th>Arsenic</th>
<th>Selenium</th>
<th>Units</th>
<th>Source</th>
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<tbody>
<tr>
<td>Cigarette</td>
<td>1R6F</td>
<td>HCI</td>
<td>4.68</td>
<td>76.1</td>
<td>BLQ</td>
<td>BLD</td>
<td>BLD</td>
<td>BLD</td>
<td>BLD</td>
<td>ng/cig</td>
<td>JACCARD et al. (342)</td>
<td></td>
</tr>
<tr>
<td>Cigarette</td>
<td>3R4F</td>
<td>HCI</td>
<td>4.92</td>
<td>93.2</td>
<td>BLQ</td>
<td>BLD</td>
<td>BLD</td>
<td>BLD</td>
<td>BLD</td>
<td>ng/cig</td>
<td>JACCARD et al. (342)</td>
<td></td>
</tr>
<tr>
<td>EC Gen 1</td>
<td>Various</td>
<td>70 / 1.8 / 10&lt;sup&gt;c&lt;/sup&gt;</td>
<td>150</td>
<td>N/A</td>
<td>0.01–0.22</td>
<td>0.03–0.57</td>
<td>N/A</td>
<td>0.11–0.29</td>
<td>N/A</td>
<td>N/A</td>
<td>μg/150 puffs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GONIEWICZ et al. (44)</td>
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<tr>
<td>Cig-a-like</td>
<td>10</td>
<td>N/A</td>
<td>N/A</td>
<td>0.017</td>
<td>0.007</td>
<td>0.05</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>μg/10 puffs&lt;sup&gt;a&lt;/sup&gt;</td>
<td>WILLIAMS et al. (123)</td>
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<tr>
<td>EC Gen 2/3</td>
<td>Open tank</td>
<td>N/A</td>
<td>0.05–0.16</td>
<td>6.88–541</td>
<td>0.39–15.6</td>
<td>1.32–2148</td>
<td>0.1–1.59</td>
<td>N/A</td>
<td>N/A</td>
<td>μg/kg&lt;sup&gt;a&lt;/sup&gt;</td>
<td>ZHAO et al. (130)</td>
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<tr>
<td>EC Gen 3</td>
<td>Liquids in reference</td>
<td>CRM81</td>
<td>N/A</td>
<td>&lt; 0.06</td>
<td>&lt; 0.05–0.12</td>
<td>&lt; 0.09–1.58</td>
<td>&lt; 1.08–1.54</td>
<td>&lt; 0.12–1.33</td>
<td>N/A</td>
<td>ng/puff&lt;sup&gt;a&lt;/sup&gt;</td>
<td>BELUSHKIN et al. (116)</td>
<td></td>
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<td>EC Gen 4</td>
<td>Closed system</td>
<td>myblu&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>BLD</td>
<td>BLD</td>
<td>0.00024</td>
<td>μg/puff</td>
<td>O’CONNELL et al. (343)</td>
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</table>

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**Abbreviations:**
- BLD: below limit of detection
- BLQ: below limit of quantification
- CRM81: CORESTA recommended method number 81
- EC: electronic cigarette
- EC Gen: electronic cigarette generation
- HCl: Health Canada intense machine smoking regime
- N/A: not analyzed
- μg/kg<sup>a</sup>: (μg/kg) in 150 puffs
- μg/10 puffs<sup>a</sup>: (μg/10 puffs) in 150 puffs
- μg/puff<sup>a</sup>: (μg/puff) in 150 puffs

<sup>a</sup> Median
<sup>b</sup> tobacco flavour, 1.6% nicotine
<sup>c</sup> puff volume / duration / interval
Table 2. Comparison of carbonyl levels in e-cigarette vapour versus cigarette smoke from published studies.

<table>
<thead>
<tr>
<th>Category</th>
<th>Device/Cigarette</th>
<th>Regime</th>
<th>No. of puffs</th>
<th>Carbonyls</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Formaldehyde</td>
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<tr>
<td>Cigarette</td>
<td>1R6F</td>
<td>HCI</td>
<td>9.1</td>
<td>4.879</td>
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<td>Benson &amp; Hedges Sky Blue</td>
<td>HCI</td>
<td>8.1</td>
<td>5.235</td>
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<tr>
<td>EC Gen1</td>
<td>Various</td>
<td></td>
<td>70 / 1.8 / 10*</td>
<td>150</td>
</tr>
<tr>
<td>EC Gen 2</td>
<td>Various open tank</td>
<td></td>
<td>55 / 4 / 30*</td>
<td>10</td>
</tr>
<tr>
<td>EC Gen 2/3</td>
<td>Open tank/ NHOSS “Lounge” model   (no nic./16 mg/mL nic.)</td>
<td>CRM81</td>
<td>96</td>
<td>0.37–1.48</td>
</tr>
<tr>
<td>EC Gen 3/4</td>
<td>ePen</td>
<td>CRM81</td>
<td>122</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>JUUL rich tobacco (20 mg/mL)</td>
<td>CRM81</td>
<td>112</td>
<td>76</td>
</tr>
<tr>
<td></td>
<td>JUUL rich tobacco (18 mg/mL)</td>
<td>CRM81</td>
<td>11</td>
<td>12</td>
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<tr>
<td>EC Gen 4</td>
<td>myblu (tobacco flavour, 1.6% nic.)</td>
<td>CRM81</td>
<td>150</td>
<td>&lt; 2.63</td>
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<tr>
<td></td>
<td>Vype ePen 2 (18 mg/mL nic.)</td>
<td>CRM81</td>
<td>268</td>
<td>230</td>
</tr>
<tr>
<td></td>
<td>Vype ePen 3 (BAT 18 mg/mL nic.)</td>
<td>CRM81</td>
<td>52.8</td>
<td>NQ</td>
</tr>
</tbody>
</table>

* Puff volume / duration / interval

Abbreviations:
- BLD: below limit of detection
- LOQ: limit of quantitation
- CRM81: CORESTA Recommended Method No. 81
- EC: electronic cigarette
- EC Gen: electronic cigarette generation
- HCI: Health Canada intense machine smoking regime
- MEK: methyl ethyl ketone
- N/A: not analysed
- Nic.: nicotine
- NQ: not quantified

Units: µg/puff or ng/mL puff
References: (22), (23), (44), (344), (113), (20), (114), (115)
Studies investigating the extent and nature of this exposure have tended to measure volatile organic compounds, CO₂, particulate matter (generally PM2.5 or PM10.0), ultrafine particles, and nicotine. Some studies have found increased concentrations of particulate matter after vaping in indoor settings (146-148), but generally conclude that exposure is lower compared to cigarette smoke (149, 150) and is less likely to be harmful to bystanders than second hand smoke (28, 29, 151-153). The absolute risk from passive exposure to EC aerosol specially in vulnerable populations, like children, pregnant women and people with impaired respiratory and cardiovascular systems, requires further assessment (151).

4.2 Toxicological assessment

As explained in the product stewardship section (see p. 66-67), robust toxicological approaches guided by regulation are essential to screen ingredients and complex mixtures (92, 154). In the screening phase, in silico approaches can be useful to identify hazards from known substances in e-liquids and to estimate toxicity of substances for which toxicological profiles are not well characterised (155). ZARINI et al. (156) used an in silico approach to develop quantitative structure-activity relationship models from data in the literature and toxicological databases in order to prioritize e-liquid ingredients according to potential acute toxicity. They used this approach to classify 264 e-liquid ingredients and flavours according to European classification on labelling and packaging criteria and recommended this method to generate information for use in a weight-of-evidence approach (156).

Substances of potential concern identified through in silico toxicology should be investigated by in vitro and in vivo methods, including toxicological assays where appropriate, to calculate thresholds of concern (157). The US FDA still recommends in vivo studies when assessing acute effects in the respiratory system (158). THE EUROPEAN CHEMICALS AGENCY (ECHA) (159) favours a weight-of-evidence approach, reflecting changing attitudes and laws in multiple countries about moving toxicology analysis away from animal testing towards innovative high-throughput and cell-culture platforms. In vitro studies range from traditional toxicological models adapted from smoke exposure studies (160) to three-dimensional cell-culture models that recreate organotypic tissue (161, 162). Multiple studies have investigated acute and chronic toxicological risk of ECs (163, 164), including testing for mutagenicity (91, 115, 165-167), cytotoxicity (potency) (91, 115, 168-171), genotoxicity (91, 115, 172-174), oxidative stress (175, 176), and wound healing (177).

Traditional toxicological tests yield complex results and are affected by variability found between and within cell lines, limited translatability to the in vivo assays, and a lack of benchmarks to contextualize the findings (171, 178). Additionally, results might be affected by the diversity of EC designs, as found in a critical review of toxicological in vivo and in vitro studies by WANG et al. (164). Overall, though, the weight of evidence indicates that ECs present lower risks to users and bystanders than conventional cigarettes (179).

Broader toxicological approaches, such as systems toxicology, may be applied. Systems toxicology employs data from techniques like transcriptomics or proteomics from exposed cells to investigate pathways involved in oxidative stress, inflammation, cell proliferation, or DNA damage, and may highlight previously unidentified potential risks (180-183).

Computational risk assessment methodologies have been proposed to compare cancer potencies across tobacco products (47, 184). Cancer potency can be calculated from EC chemical emissions data and enable comparisons between products by factoring consumer exposure to different products. STEPHENS (47) suggested that ECs only have 0.004 times the carcinogenicity of cigarette smoke whilst still being 10.7 times more carcinogenic than nicotine inhalers.

4.3 Assessment of clinical and health effects of vaping

Smoking increases health risks to cardiovascular, respiratory, and other systems soon after the onset of smoking, with the risks of death, disease, and disability rising with increasing duration of use. However, these excess risks are largely reversible with smoking cessation (7). Acute measurements of circulation and lung function may improve within 3-9 months of quitting, and coronary heart disease excess risk due to smoking is halved after 1 year and completely reversed by around 15 years (2, 185). The aim of assessing clinical effects of smoking, therefore, is not only to investigate damage caused but also to assess whether changing behaviour can reduce these excess risks and/or lead to functional benefits.

4.3.1 Nicotine pharmacokinetic studies

Satisfactory nicotine delivery is critical to the acceptability of ECs. Despite the popularity of later-generation ECs, many users relapse to smoking alone or alongside EC use (dual use) raising concerns about the viability of ECs as a long-term alternative to cigarettes (186-189). Data from 1,489 current adult smokers reported they discontinued using ECs mostly because the experience was not close enough to smoking and cravings were not reduced (189). Later-generation EC designs have attempted to address these issues through use of higher power, improved coil heating elements, and nicotine delivery without irritation (190).

Pharmacokinetic clinical trials are often used to investigate safety, nicotine delivery, and acceptability of ECs. These studies assess the likelihood of product-related adverse effects, describe the concentration-time profile for nicotine, and provide insights into the relationship between nicotine concentration and specific responses (e.g., urge for product, craving, and product liking/satisfaction). Pharmacokinetic endpoints estimated from these studies can be used to make comparisons between different EC products and with other product classes (e.g., combustible cigarettes and nicotine replacement therapies (NRTs)).

The average maximum concentration (C_{max}) of nicotine with smoking is 10-21 ng/mL, depending on the “tar” and nicotine yield of the cigarette (191-197). For NRT, C_{max} is generally in the range 2-18 ng/mL, depending on the
nicotine concentration, type of device, and usage (198-200). Early pharmacokinetic studies using first-generation (cig-a-like) ECs with similar nicotine concentrations to NRT and a fixed puffing protocol for 5 min reported C_{max} of 1.3-17 ng/mL (201-203). Second- and third-generation ECs improved nicotine delivery under similar conditions (C_{max} 4-12.8 ng/mL) (100, 201, 204-206). Fourth-generation ECs using protonated nicotine have substantially lessened or even closed the nicotine bioavailability gap between cigarette smoke and EC vapour (139, 207, 208). For instance, EBAJEMITO et al. (139) assessed nicotine delivery in participants who switched from smoking to vaping at several nicotine concentrations and with and without nicotine salts. The C_{max} for e-liquid (30 mg/mL nicotine) containing nicotine salt reached 14.1 ng/mL compared with 14.5 ng/mL for a 7-mg ISO “tar” cigarette. Another study conducted by O’CONNELL et al. (140) found a similar delivery profile for an EC containing a 40-mg nicotine lactate e-liquid formulation. Product use also has an impact on nicotine delivery, with more experienced users achieving greater nicotine concentrations (209, 210). Finally, satisfaction with e-liquid formulations containing nicotine might be limited by sensorial aspects, as nicotine content and flavour strength seem to correlate with harshness or throat irritation and perception of bitterness (51). Together, these findings could explain the results from some studies suggesting that ECs are more successful than NRT in providing smokers a satisfactory alternative to cigarettes (211, 212). Table 3 summarises some of the findings from Pharmacokinetic studies according to EC type/generation.

4.3.2 Biomarkers of exposure

Biomarkers of exposure (BoEs) to cigarette smoke have long been used to assess the effects of tobacco consumption. Exposure to nicotine and aerosol toxicants is assessed by measurement of nicotine metabolites and toxicant concentrations in biological samples, most often in urine. In most EC studies, reductions in toxicant exposure are benchmarked against cigarette smoke and, therefore, the panels of BoEs are based on compounds known to be present in cigarette smoke. The FDA workshop identified the measurement of BoE for nicotine and 19 HPHCs, including nicotine and tobacco alkaloids, carbon monoxide, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, volatile organic compounds, carcinogenic aromatic amines, and metals (213). Multiple studies have assessed changes in BoEs after study participants’ exposure to EC aerosol (Table 4). In interventional studies, which are generally randomised studies, participants are assigned to use a small number of products or different categories of products (214-217). Observational studies are often larger and assess products chosen or already used by the consumers (218-221). Interpretation and extrapolation of results from some randomised studies has been hindered by lack of appropriate descriptions of products used in the study (222), exclusion of appropriate controls to provide context (215, 217), and small sample sizes that limit generalisability (216, 222). Some of the larger and longer-term studies provide a clearer picture. In a switching study of 153 smokers who switched from cigarettes to a cig-a-like EC or nicotine gum, ROUND et al. (223) assessed a comprehensive panel of BoEs. They found significant reductions across all BoEs in the EC arm, while nicotine levels were higher than in those using nicotine gum. A cross-sectional study by SHAHAB et al. (221) compared exposure to carcinogens and toxicants in long-term smokers with those in former smokers who had used ECs or NRT exclusively for at least 6 months and in dual users who had smoked combustible cigarettes plus used ECs or NRT for at least 6 months. The sample size was 181, with 36-37 in each group. Nicotine intake was similar for all study groups, but BoE concentrations were significantly lower in the exclusive NRT and EC groups than in any group including smokers. NNAL, a BoE associated with lung cancer, was lower in the EC only group than in all other groups. WALELE et al. (224) performed a 2-year ambulatory study as continuation of a 12-week residential study in which smokers had switched to a cig-a-like EC or continued smoking (225). They compared changes in BoE to acrolein, benzene, and NNK over time in 209 participants. BoE concentrations among smokers who switched to the EC fell substantially within roughly 1 month and remained at similar levels over 2 years. A very large cross-sectional biomarker analysis based on the US PATH observational study, with biomarker data for more than 5,000 participants classified as smokers, EC users, dual users, and never tobacco users showed lower BoE levels of tobacco-specific nitrosamines in the EC users group than in smokers (219). Exposure to metals, such as beryllium, cadmium, and lead, were lower in EC users than in cigarette smokers but higher than in never tobacco users. There were no differences across groups for cobalt, manganese, or thallium. All seven BoEs for polycyclic aromatic hydrocarbons and 17 of 20 volatile organic compounds BoEs were significantly higher in smokers than in the other groups. In a comparison of exclusive smokers and exclusive EC users, levels of exposure to total NNAL and carbon monoxide were significantly lower in vapers, including below the level of detection in 30% of cases (206). There is also some evidence of reversibility of effects in ex-smokers who had switched entirely to ECs for at least 2 months (226). GONiewicz et al. (215) evaluated seven nicotine metabolites and 17 BoEs in urine samples of 20 cigarette smokers before and after switching exclusively to ECs for 2 weeks and found significantly reduced concentrations of 12 of the biomarkers following switching. Large observational studies are more representative in terms of demographics and the EC category (219, 227). However, assessment of usage patterns can be complex in ambulatory studies yet not reflect real-world use in confinement settings where product use can be controlled. In all studies, especially large observational studies, the numbers of BoEs that may be assessed might be hampered by resource availability. Overall, measurement of BoEs appears to reflect toxicant delivery differences observed in chemistry assessments.
<table>
<thead>
<tr>
<th>Reference</th>
<th>Product type (nicotine concentration)</th>
<th>Pharmacokinetic parameters</th>
<th>Pharmacodynamic parameters</th>
<th>Vital signs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C\text{max} (ng/mL)</td>
<td>T\text{max} (min)</td>
<td>AUC (ng•min/mL)</td>
</tr>
<tr>
<td><strong>Combustible cigarettes</strong></td>
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<tr>
<td>DIGARD et al., 2013 (195)</td>
<td>Lucky Strike Red (14.6 mg)</td>
<td>12.8</td>
<td>7.20</td>
<td>14.8</td>
</tr>
<tr>
<td>YAN &amp; D’RUIZ, 2015 (345)</td>
<td>Marlboro Gold King Size (0.8 mg)</td>
<td>15.84–29.23</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>EBRAJEMITO et al., 2020 (139)</td>
<td>Benson &amp; Hedges Sky Blue (7 mg ISO tar)</td>
<td>14.5 (ad libitum)</td>
<td>5.00</td>
<td>660.0</td>
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<td><strong>First-generation e-cigarettes (cig-a-like)</strong></td>
<td></td>
<td></td>
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<tr>
<td>HAJEK et al., 2017 (346)</td>
<td>Vuse (48 mg/mL); Gamucci (16 mg/mL); Blu (18 mg/mL); Vype (16.8 mg/mL); E-lites (24 mg/mL); Puritane (20 mg/mL)</td>
<td>13.6</td>
<td>4.0</td>
<td>244.9</td>
</tr>
<tr>
<td>BULLEN et al., 2010 (198)</td>
<td>Ruyan V8 (16 mg/mL)</td>
<td>1.3</td>
<td>19.6</td>
<td>N/A</td>
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<tr>
<td>VANSICKEL et al., 2010 (347)</td>
<td>NJOY NPRO (18 mg/mL); Hydro (16 mg/mL)</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td>NIDES et al., 2014 (202)</td>
<td>NJOY King Bold (26 mg/mL)</td>
<td>3.5–5.1</td>
<td>30 s–30 min</td>
<td>0.67–0.57</td>
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<tr>
<td></td>
<td></td>
<td>C&lt;sub&gt;max&lt;/sub&gt; (ng/mL)</td>
<td>Tmax (min)</td>
<td>AUC (ng•min/mL)</td>
</tr>
<tr>
<td>YAN &amp; D'RUIZ, 2015 (345)</td>
<td>Blu (16 mg/mL, two formulations); Blu (24 mg/mL, three formulations)</td>
<td>10–17</td>
<td>N/A</td>
<td>N/A</td>
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<tr>
<td>FARSALINOS et al., 2014 (201)</td>
<td>V2 (18 mg/mL)</td>
<td>2.0 (fixed puff) and (ad libitum)</td>
<td>N/A</td>
<td>N/A</td>
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<td>VOOS et al., 2019 (348)</td>
<td>V2 (11.7 mg/mL) Green smoke (19.4 mg/mL)</td>
<td>4.07</td>
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<td>88.60</td>
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<td>Second-generation e-cigarettes</td>
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<td>VOOS et al., 2019 (348)</td>
<td>Mod iTazte (29.9 mg/mL)</td>
<td>6.6</td>
<td>10</td>
<td>272.3</td>
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<tr>
<td>HAJEK et al., 2017 (346)</td>
<td>KangerTech EVOD (20 mg/mL)</td>
<td>9.9</td>
<td>6.0</td>
<td>200.6</td>
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<td>Third-generation e-cigarettes</td>
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<td>FARSALINOS et al., 2014 (201)</td>
<td>EVIC device with EVOD cartomizer (18 mg/mL)</td>
<td>4.00 (defined) 21.0 (ad libitum)</td>
<td>N/A</td>
<td>N/A</td>
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<td>HAJEK et al., 2017 (346)</td>
<td>Innokin (20 mg/mL)</td>
<td>11.9</td>
<td>6</td>
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<td>VOOS et al., 2019 (348)</td>
<td>eGO V2 Pro (29.9 mg/mL)</td>
<td>5.52</td>
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<td>121.9</td>
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Table 3. Continued.

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<td>T&lt;sub&gt;max&lt;/sub&gt; (min)</td>
<td>AUC (ng∙min/mL)</td>
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<td>EBJEMITO et al., 2020 (139)</td>
<td>Vype ePen (18 mg/mL)</td>
<td>4.79</td>
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<td>Fourth-generation e-cigarettes</td>
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<tr>
<td>O'CONNELL et al., 2019 (140)</td>
<td>myblu 25 mg/mL (free-base); myblu 16 mg/mL (salt); myblu 25 mg/mL (salt); blu PRO 48 mg/mL (salt)</td>
<td>5.05</td>
<td>8.03</td>
<td>99.99</td>
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<td>Vype ePen3 18 mg/mL (freebase; ad lib); Vype ePen3 18 mg/mL (med salt; ad lib); Vype ePen3 30 mg/mL (high salt; ad lib); Vype ePen3 18 mg/mL (med salt; fixed puff); Vype ePen3 12 mg/mL (low salt; ad lib)</td>
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<td>Nicotine-replacement therapy</td>
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<td>DIGARD et al., 2013 (195)</td>
<td>Nicotine gum (4.2 mg)</td>
<td>9.10</td>
<td>45.0</td>
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<tr>
<td>LUNELL &amp; CUR-</td>
<td>Nicotine Polarilex gum (4 mg)</td>
<td>12.8</td>
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<td>3190</td>
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<td>VALL, 2011 (349)</td>
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<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$T_{\text{max}}$ (min)</td>
<td>AUC (ng•min/mL)</td>
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<td>Dautzenberg et al., 2007 (350)</td>
<td>1 mg Nicotinell lozenges</td>
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<td>2 mg Nicotinell lozenges</td>
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<td>48.0</td>
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<td>2 mg Nicorette gum</td>
<td>2.90</td>
<td>48.0</td>
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<td>Choi et al., 2003 (351)</td>
<td>4 mg nicotine lozenges</td>
<td>10.8</td>
<td>66.0</td>
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<td>4 mg nicotine gum</td>
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<td>54.0</td>
<td>34.6 *</td>
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<td>Hansson et al., 2017 (199)</td>
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<td>13.8</td>
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<td></td>
<td>4 mg nicotine gum</td>
<td>10.1</td>
<td>30.0</td>
<td>30.2 *</td>
</tr>
<tr>
<td></td>
<td>2 mg nicotine gum</td>
<td>5.90</td>
<td>30.0</td>
<td>17.1 *</td>
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<td>4 mg nicotine lozenge</td>
<td>9.30</td>
<td>45.0</td>
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<td>1 mg nicotine mouth spray</td>
<td>3.30</td>
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<td>5.30</td>
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<tr>
<td>Kraiczi et al., 2011 (352)</td>
<td>4 mg nicotine mouth spray</td>
<td>9.10</td>
<td>10.0</td>
<td>23.7</td>
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<td>4 mg nicotine lozenge</td>
<td>7.00</td>
<td>45.0</td>
<td>24.3</td>
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<td>4 mg nicotine gum</td>
<td>7.80</td>
<td>30.0</td>
<td>21.1</td>
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<td>4 mg lozenges prototype I</td>
<td>18.18</td>
<td>66.0</td>
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</tr>
<tr>
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<td>4 mg lozenges prototype II</td>
<td>18.11</td>
<td>66.0</td>
<td>85.69 *</td>
</tr>
<tr>
<td>Sukhua et al., 2018 (200)</td>
<td>4 mg lozenges prototype III (I, II, III had different dissiputions)</td>
<td>17.11</td>
<td>66.0</td>
<td>84.59 *</td>
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<td></td>
<td>4 mg Nicorette lozenges</td>
<td>18.67</td>
<td>66.0</td>
<td>90.03 *</td>
</tr>
<tr>
<td>Mlander &amp; Lunell, 2001 (353)</td>
<td>2 mg nicotine sublingual tablet</td>
<td>13.2</td>
<td>20</td>
<td>12.4 *</td>
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<tr>
<td></td>
<td>2 mg Nicorette gum</td>
<td>14.4</td>
<td>20</td>
<td>13.5</td>
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<tr>
<td>Lunell et al., 2020 (354)</td>
<td>4 mg Nicorette gum</td>
<td>12.8</td>
<td>46.0</td>
<td>52.1</td>
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<td>Reference</td>
<td>Product type (nicotine concentration)</td>
<td>Pharmacokinetic parameters</td>
<td>Pharmacodynamic parameters</td>
<td>Vital signs</td>
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<tr>
<td></td>
<td></td>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>$T_{\text{max}}$ (min)</td>
<td>AUC (ng•min/mL)</td>
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<td>BULLEN et al. (198)</td>
<td>Nicorette inhalator (10 mg)</td>
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<td>Fixed puff</td>
<td>JUUL 59 mg/mL with silica wick</td>
<td>9.3</td>
<td>6.2</td>
<td>5.0 *</td>
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<tr>
<td></td>
<td>JUUL 18 mg/mL with silica wick</td>
<td>3.2</td>
<td>6.3</td>
<td>1.7 *</td>
</tr>
<tr>
<td></td>
<td>JUUL 18 mg/mL with cotton wick</td>
<td>3.3</td>
<td>5.8</td>
<td>1.8 *</td>
</tr>
<tr>
<td></td>
<td>JUUL 9 mg/mL with cotton wick</td>
<td>2.1</td>
<td>6.6</td>
<td>1.2 *</td>
</tr>
<tr>
<td>GOLDENSON et al. (355)</td>
<td>Ad libitum puff</td>
<td>59 mg/mL silica wick provided highest level of satisfaction followed by 18 mg/mL silica wick, 18 mg/mL coil wick and 9 mg/mL coil wick</td>
<td>59 mg/mL silica wick provided highest level of satisfaction followed by 18 mg/mL silica wick, 18 mg/mL coil wick and 9 mg/mL coil wick</td>
<td>59 mg/mL silica wick provided highest level of satisfaction followed by 18 mg/mL silica wick, 18 mg/mL coil wick and 9 mg/mL coil wick</td>
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<tr>
<td></td>
<td>JUUL 59 mg/mL with silica wick</td>
<td>8.3</td>
<td>6.4</td>
<td>4.6 *</td>
</tr>
<tr>
<td></td>
<td>JUUL 18 mg/mL with silica wick</td>
<td>3.5</td>
<td>6.5</td>
<td>1.8 *</td>
</tr>
<tr>
<td></td>
<td>JUUL 18 mg/mL with cotton wick</td>
<td>3.3</td>
<td>7.1</td>
<td>2.1 *</td>
</tr>
<tr>
<td></td>
<td>JUUL 9 mg/mL with cotton wick</td>
<td>2.3</td>
<td>6.7</td>
<td>1.2 *</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- BP = blood pressure
- $C_{\text{max}}$ = maximum concentration
- EC = electronic cigarette
- $T_{\text{max}}$ = time to maximum concentration
- bpm = beats per minute
- PK = pharmacokinetic
- AUC = area under the curve
- N/A = not analyzed
- * Reported in ng•h/mL
Table 4. Clinical studies of e-cigarettes.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design/product</th>
<th>Study arms (subgroups)</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHAHAB et al., 2017b (221)</td>
<td>Cross-sectional study, using unspecified EC or NRT products for ≥ 6 months</td>
<td>Smokers (n = 37) Dual use NRT (n = 36) Dual use EC (n = 36) NRT (n = 36) EC (n = 36)</td>
<td>NNAL, 3HPMA, AAMA, CYMA, MHBMA3, HEMA were expressed as proportions of levels in the smoker arm. Significantly lower levels of all biomarkers were observed for EC only users (2.9–43.5% decrease) that were similar to those in NRT only users. NRT and EC dual users presented similar biomarker levels to the smoking group.</td>
</tr>
<tr>
<td>LORKEWICZ et al., 2019 (216)</td>
<td>Cross-sectional study, using unspecified ECs or smokeless products</td>
<td>No tobacco (n = 12) ECs (n = 12) smokers (n = 12) smokeless tobacco (n = 12)</td>
<td>The EC users showed higher levels of xylene, cyanide, styrene, ethylbenzene, and acrolein metabolites than non-tobacco users, but lower levels for toluene and acrolein metabolites. Levels of VOC metabolites in the smokeless tobacco group were similar to those in the non-tobacco group.</td>
</tr>
<tr>
<td>CZOLI et al., 2019 (214)</td>
<td>Three-period crossover design where dual users (smoked ≥ 5 cigarettes per day and used an EC at least once a day for the past 7 days) to either EC &gt; smoking &gt; no tobacco or smoking &gt; EC &gt; no tobacco, with each condition lasting for 7 days</td>
<td>Dual users (n = 48)</td>
<td>1-HOP was significantly higher during the smoking period than during dual use but was lower during EC use, NNAL levels decreased significantly from dual use, by 30% during EC use and by 35% during cessation but did not change during smoking.</td>
</tr>
<tr>
<td>HECHT et al., 2015 (226)</td>
<td>Cross-sectional study comparing biomarker levels in smoker to ECs switchers (≥ 2 months) with those in smokers from three previously published studies (CARMELLA et al. 2009; HATSUKAMI et al. 2010; ZARTH et al. 2014)</td>
<td>EC users (n = 28)</td>
<td>All biomarkers (1-HOP, total NNAL, 3HPMA, 2HPMA, HMPMA, and SPMA) were significantly lower in EC users than in smokers.</td>
</tr>
<tr>
<td>MCOBBIE et al., 2015 (217)</td>
<td>Switching study in which smokers switched to ECs or dual use</td>
<td>EC users (n = 16) Dual use (n = 18)</td>
<td>3HPMA in urine showed significant reductions at 4 weeks after switching compared with baseline (ECs 79%, dual use 60%).</td>
</tr>
<tr>
<td>GONEVICK et al., 2017 (215)</td>
<td>Switching study in which smokers switched to ECs dual use for 2 weeks then ECs only for 2 weeks</td>
<td>Smokers switching to ECs (n = 20)</td>
<td>Significant reductions were seen after 2 weeks in urine biomarkers of exposure to NNAL and eight VOC metabolite levels (50–69%) and fluorene (42–82%), but not in those for pyrene, phenanthrene, and naphthalene.</td>
</tr>
<tr>
<td>CRAVO et al., 2016 (225)</td>
<td>Parallel study in which smokers were randomly assigned in a ratio of 3:1 to switch to an EC (tobacco or menthol flavour) or continue smoking for 12 weeks</td>
<td>Switch to EC (n = 306) continue smoking (n = 102)</td>
<td>After 12 weeks, 3-HPMA, S-PMA and total NNAL in urine were reduced by around 30% compared with baseline in those who switched to ECs, whereas no reductions were among those who continued smoking.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design/product</td>
<td>Study arms (subgroups)</td>
<td>Conclusions</td>
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<tr>
<td>O’CONNELL et al., 2016</td>
<td>Parallel study of smokers switching to ECs or dual use during 6 days in clinic</td>
<td>Rechargeable EC tobacco flavour (n = 15) rechargeable EC cherry flavour (n = 15) disposable EC cherry flavour (n = 15) dual use with rechargeable EC tobacco flavour (n = 15) dual use with rechargeable EC cherry flavour (n = 15) dual use with disposable EC cherry flavour (n = 15) cessation (n = 15)</td>
<td>Biomarkers: all urine biomarker measures (total NNAL, 3-HPMA, HMPMA, CEMA, 1-OHP, NNN, MHBMA, S-PMA) were significantly reduced compared to baseline in all groups, except MHBMA in the cherry disposable dual use group; levels in dual users were significantly higher than those in the cessation group. Spirometry: small changes seen in FVC from baseline to Day 5 (-0.5% to 3.1%) but were significant for tobacco and cherry rechargeable EC only users, while FEV1 changes (-1.5% to 6.0%) were significant increases for the tobacco and cherry rechargeable EC only users and cherry rechargeable dual users. Exhaled CO: reduced across all study groups, by around 89% in EC only and cessation groups and around 26% in dual user groups. Exhaled FeNO: increased by 45.8–63.4% in EC only groups and 55% in the cessation group, but not in dual user groups (differences from the tobacco rechargeable and cherry disposable EC only groups were significant). Systolic blood pressure: changes varied across groups, but significant reductions in mornings seen for cherry flavour dual users, and in rechargeable tobacco EC only users. Diastolic blood pressure: reduced significantly in mornings for rechargeable tobacco dual users and cherry rechargeable EC only users. Heart rate: reductions observed in the cessation group, rechargeable tobacco EC only group and rechargeable cherry product EC only and dual use groups.</td>
</tr>
<tr>
<td>D’RUIZ et al., 2017</td>
<td>Cross-sectional study of age and gender matched participants, assessing spot urine samples from EC users, smokers and non-smokers for metals (antimony, cadmium, copper, indium, lead, nickel, rubidium, selenium, silver, titanium, and zinc), metal exposure, and BOPH</td>
<td>EC users (n = 20) smokers (n = 13) non-smokers (n = 20)</td>
<td>Metals: biomarkers for selenium were significantly higher in EC users than in non-smokers or smokers with means 54.0, 41.8, and 36.7 μg/g creatinine, respectively, and were significantly increased for zinc in EC users compared to non-smokers (584.5 vs 413.6 mg/g creatinine) but not compared to smokers (470.7 mg/g creatinine). Metal exposure: metallothionein was significantly greater in EC users than in non-smokers (mean 3761 vs 1129 pg/mg creatinine) but similar to that in smokers (4096 pg/mg creatinine). BOPH: concentrations were increased in EC users when compared to non-smokers but not smokers (8-OHdG 442.8 vs 221.6 and 388 ng/mg creatinine; 8-isoprostane 750.8 vs 411.2 and 784.2 ng/mg creatinine).</td>
</tr>
<tr>
<td>D’RUIZ et al., 2016</td>
<td>Longitudinal study (52 weeks) of smokers switching to ECs with different concentrations of nicotine</td>
<td>2.4% nicotine (n = 49) 1.8% nicotine (n = 50) 0% nicotine (n = 40)</td>
<td>82 participants continued smoking, 34 significantly reduced the number of cigarettes smoked, and 18 quit smoking after switching. Exhaled CO: decreased significantly in quitters and smokers who reduced cigarette consumption from week 12. Exhaled FeNO: increased significantly in quitters from week 12. FEV1, FVC, and FEV1/FVC ratio not affected by smoking status (continued, reduced, or quit). FEV1/FVC% significantly increased among quitters.</td>
</tr>
<tr>
<td>SAKAMAKI-CHING et al., 2020</td>
<td>Retrospective chart review study of changes in respiratory outcomes over 2 years in patients with COPD who were daily EC users (without combustible cigarettes) or smokers, matched for age and sex</td>
<td>Baseline COPD GOLD stage 1 (smokers n = 3; EC users n = 2) stage 2 (smokers n = 5; EC users n = 6) stage 3 (smokers n = 11; EC users n = 10) stage 4 (smokers n = 5; EC users n = 6)</td>
<td>FEV1, FVC and ratio FEV1/FVC did not change from baseline values in either EC users or smokers, whereas COPD exacerbations were reduced and 6-min walking test scores increased compared with baseline in the EC users group but not the smoking group.</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design/product</td>
<td>Study arms (subgroups)</td>
<td>Conclusions</td>
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<tr>
<td>PULVERS et al.,</td>
<td>Switch study of smokers switching to an EC for 30 days with choice of seven flavours and two nicotine concentrations (12 or 24 mg/mL)</td>
<td>Smokers (n = 37)</td>
<td>Cigarette consumption: decreased significantly from mean 24.8 days to 14.0 days per month and mean 8.7 to 4.4 cigarettes per day, with six participants quitting, 21 becoming dual users and the remaining 10 sporadic EC only users</td>
</tr>
<tr>
<td>2018 (358)</td>
<td></td>
<td></td>
<td>Biomarkers: NNAL, PMA, CNEMA decreased significantly from baseline, whereas HEMA, MMA, 3-HPMA, 2-HPMA, AAMA and HPMMA did not</td>
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<tr>
<td></td>
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<td></td>
<td>Exhaled CO: decreased significantly</td>
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<td></td>
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<td>Smoking dependence: decreased significantly from baseline</td>
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<tr>
<td>AHERRERA et al.,</td>
<td>Cross sectional study of nickel and chromium concentrations in EC users</td>
<td>EC users (n = 59)</td>
<td>Concentrations in urine, saliva, and breath: were below the limit of detection for nickel in 4.7%, 3.2% and 3.1% of samples, respectively, and for chromium in 7.8%, 1.6% and 56.3% of samples</td>
</tr>
<tr>
<td>2017 (218)</td>
<td></td>
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<td>Weekly consumption, time to first vape, voltage of device, number of coil changes per month, and levels in aerosol, dispenser, and tank had effects</td>
</tr>
<tr>
<td></td>
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<td>Nickel concentrations in urine were associated with time to first vape, coil changes, and concentrations in aerosol, tank, and in breath showed no associations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chromium in saliva was associated with cotinine in urine and concentrations in aerosol, tank, and dispenser</td>
</tr>
<tr>
<td>WIESLANDER et al.,</td>
<td>Symptoms study after experimental exposure of healthy non-asthmatic volunteers to propylene glycol mist for 1 min</td>
<td>Healthy volunteers (n = 27)</td>
<td>Symptom VAS ratings: showed significant increase of ocular irritation, throat irritation, and dyspnoea but no effects on solvent smell or other symptoms</td>
</tr>
<tr>
<td>2001 (231)</td>
<td></td>
<td></td>
<td>Lung function: FEV1, FVC, FEV1/FVC ratio, PEF did not change significantly from before to after exposure</td>
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<td>Tear film stability: break-up time decreased significantly after exposure from 38 to 28 s</td>
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<td>Dose response: throat dryness was 47% in the low exposure group but 100% in the high exposure group, where VAS ratings were also higher</td>
</tr>
<tr>
<td>Reference</td>
<td>Study design/product</td>
<td>Study arms (subgroups)</td>
<td>Conclusions</td>
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</tr>
<tr>
<td>GONIEWICZ et al.,</td>
<td>Cross-sectional analysis of population in longitudinal Population Assessment of Tobacco and Health (PATH) study for biomarker concentrations</td>
<td>Smokers (n = 2411)</td>
<td>NNAL: concentrations were significantly lower in never-smokers than in EC users and in both groups compared with smokers (geometric mean 0.921 vs 4.887 and 203.5 pg/mg creatinine). Other tobacco specific nitrosamines: NAT, NAB, and NNN in EC users were above the limit of quantification for 12%, 15% and 34% of samples, respectively and were all higher than those in never tobacco users but significantly lower than those in smokers Metal exposure: beryllium was found only in 3–9% of samples; cadmium was higher in EC users than in never tobacco users (0.193 vs 0.149 ng/mg creatinine) but lower than in smokers and dual users (0.277 and 0.280 ng/mg creatinine, respectively); lead was elevated in EC users compared to never users (0.432 vs 0.351 ng/mg creatinine) but was highest in smokers and dual users (0.500 and 0.479 ng/mg creatinine, respectively); strontium differed only between dual users and smokers (130.5 vs 113.7 mg/mg creatinine); and no differences in concentrations between groups were found for cobalt, manganese or thallium Tobacco alkaloids: anabasine and anatabine concentrations were significantly lower in EC users than in dual users or smokers but similar to those in never tobacco users Total inorganic arsenic: significantly higher in EC users than in smokers and dual users (0.053 vs 0.048 and 0.045 ug/mg creatinine) but not different to never tobacco users (0.054 ug/mg creatinine) PAHs: of seven biomarkers of PAH exposure only 1-hydroxypyrene was elevated in EC users compared to never tobacco users, while all were significantly higher in smokers and five were higher in dual users VOCs: of 20 biomarkers four were significantly elevated in EC users compared with never tobacco users (AMCA 1.5 times, BMA 1.1 times, CYHA 1.3 times, and CYMA 3.0 times), although CYHA could only be detected in 3% of never tobacco users and 14% of EC users; 17 biomarkers were higher in smokers than in EC users by 1.4–31.0 times</td>
</tr>
<tr>
<td>et al., 2018 (219)</td>
<td>Cross-sectional analysis of population in longitudinal Population Assessment of Tobacco and Health (PATH) study for biomarker concentrations</td>
<td>EC users (n = 247)</td>
<td></td>
</tr>
<tr>
<td></td>
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<td>never tobacco users (n = 1655)</td>
<td></td>
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<tr>
<td>OLIVERI et al., 2020</td>
<td>Cross-sectional observational study comparing biomarkers of exposure and BOPH in ex-smoker (&lt;10 cigarettes per day for ≥10 years) EC users (&lt;6 months) with current smokers</td>
<td>Smokers (n = 62)</td>
<td></td>
</tr>
<tr>
<td>et al. (234)</td>
<td>Cross-sectional observational study comparing biomarkers of exposure and BOPH in ex-smoker (&lt;10 cigarettes per day for ≥10 years) EC users (&lt;6 months) with current smokers</td>
<td>ex-smoker EC users (n = 132)</td>
<td></td>
</tr>
<tr>
<td>Piper et al., 2019</td>
<td>Baseline assessments for longitudinal observational cohort study (2 years) of smokers versus EC dual users</td>
<td>Smokers (n = 166)</td>
<td></td>
</tr>
<tr>
<td>(227)</td>
<td>Baseline assessments for longitudinal observational cohort study (2 years) of smokers versus EC dual users</td>
<td>dual users (n = 256)</td>
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</tr>
<tr>
<td>ROUND et al., 2019</td>
<td>Randomized, controlled, open-label, forced switch parallel group study in smokers of menthol and non-menthol cigarettes who switched to an EC or nicotine gum, to measure biomarkers of exposure after 5 days</td>
<td>Smoker to EC (n = 38)</td>
<td></td>
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<tr>
<td>(223)</td>
<td>Randomized, controlled, open-label, forced switch parallel group study in smokers of menthol and non-menthol cigarettes who switched to an EC or nicotine gum, to measure biomarkers of exposure after 5 days</td>
<td>smoker to nicotine gum (n = 39)</td>
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<td>menthol smoker to menthol EC (n = 40)</td>
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<tr>
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<td>menthol smoker to nicotine gum (n = 41)</td>
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Table 4. Continued.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design/product</th>
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<th>Conclusions</th>
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<tbody>
<tr>
<td>SONG et al., 2020</td>
<td>Cross-sectional study of lung inflammation, measured by cell counts, cytokines, genome-wide gene expression and DNA methylation in bronchoalveolar lavage and brushings, in never smokers, EC users and smokers</td>
<td>Never-smokers (n = 42) EC users (n = 15) smokers (n = 16)</td>
<td>Most inflammatory cell counts and cytokine concentrations in EC users were intermediate between those of smokers and never-smokers, while most biomarkers were similar to those for never smokers, as were differential gene expression and DNA methylation</td>
</tr>
</tbody>
</table>

Abbreviations:

<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>BOPH</td>
<td>Biomarkers of potential harm</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>EC</td>
<td>Electronic cigarette</td>
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<tr>
<td>FEF_{25–75}</td>
<td>Mid-expiratory flow rate</td>
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<tr>
<td>FVC</td>
<td>Forced vital capacity</td>
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<tr>
<td>GOLD</td>
<td>Global Initiative for Chronic Obstructive Lung Disease</td>
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<tr>
<td>PAHs</td>
<td>Polycyclic aromatic hydrocarbons</td>
</tr>
<tr>
<td>PEF</td>
<td>Peak expiratory flow rate</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual analogue scale</td>
</tr>
<tr>
<td>VOC</td>
<td>Volatile organic compound</td>
</tr>
<tr>
<td>1-HOP</td>
<td>1-hydroxypyrene</td>
</tr>
<tr>
<td>2-HPMA</td>
<td>2-hydroxypropyl mercapturic acid</td>
</tr>
<tr>
<td>3-HPMA</td>
<td>3-hydroxypropyl mercapturic acid</td>
</tr>
<tr>
<td>AAMA</td>
<td>2-cyanoethylmercapturic acid</td>
</tr>
<tr>
<td>AMCA</td>
<td>N-acetyl-S-(N-methylcarbamoyl)-L-cysteine</td>
</tr>
<tr>
<td>BMA</td>
<td>S-benzylmercapturic acid</td>
</tr>
<tr>
<td>CEMA</td>
<td>2-cyanethymercapturic acid</td>
</tr>
<tr>
<td>CNEMA</td>
<td>2-cyanethymercapturic acid</td>
</tr>
<tr>
<td>COHb</td>
<td>Carboxyhemoglobin</td>
</tr>
<tr>
<td>CYHA</td>
<td>N-acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine</td>
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<tr>
<td>CYMA</td>
<td>N-acetyl-S-(2-cyanoethyl)-L-cysteine</td>
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<td>N-acetyl-S-(2-cyanoethyl)-L-cysteine</td>
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<tr>
<td>CYMA</td>
<td>N-acetyl-S-(1-cyano-2-hydroxyethyl)-L-cysteine</td>
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<td>HEMAl</td>
<td>2-hydroxyethylmercapturic acid</td>
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<td>HMPMA</td>
<td>N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine</td>
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<td>HPMA</td>
<td>N-acetyl-S-(3-hydroxypropyl-1-methyl)-L-cysteine</td>
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<tr>
<td>MHBMA</td>
<td>Monoxydroxy-3-butyl mercapturic acid</td>
</tr>
<tr>
<td>MMA</td>
<td>Methylmercapturic acid</td>
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<tr>
<td>MHBMA</td>
<td>Monoxydroxy-3-butyl mercapturic acid</td>
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<td>NAB</td>
<td>N-nitrosoanabasine</td>
</tr>
<tr>
<td>NAT</td>
<td>N-Nitrosoanatabine</td>
</tr>
<tr>
<td>NNN</td>
<td>4-(Methylnorisomino)-1-(3-pyriyl)-1-butanol</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine replacement therapy</td>
</tr>
<tr>
<td>NRT</td>
<td>Nicotine replacement therapy</td>
</tr>
<tr>
<td>NNN</td>
<td>N-nitrosomonicotone</td>
</tr>
<tr>
<td>PMA</td>
<td>Phenylmercapturic acid</td>
</tr>
<tr>
<td>S-PMA</td>
<td>S-phenylmercapturic acid</td>
</tr>
<tr>
<td>NNAL</td>
<td>4-(Methylisosamino)-1-(3-pyriyl)-1-butanol</td>
</tr>
</tbody>
</table>

* Biomarkers of exposure to *N,N*-dimethylformamide, isocyanates, toluene, and acrylonitrile.
4.3.3 Biomarkers of potential harm

Disease-associated biomarkers known as biomarkers of potential harm (BoPHs) could provide valuable information characterising the risk of tobacco products. BoPHs were defined by the Institute of Medicine as the "measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm; also includes 'preclinical changes'" (11). CHANG et al. (228) describe in detail BoPH in the context of tobacco product assessment as well as the types of BoPHs identified during this FDA public workshop. Table 4 also summarizes results from studies evaluating biomarkers of potential harm.

Usability of BoPHs to characterize risk associated with ECs is underpinned by reversibility of smoking harm achieved through complete cessation of tobacco products. Most clinical studies compare disease-associated BoPHs in vapers against those in smokers and a cessation group used as a reference. Many BoPHs are not smoking specific or even disease specific, so contextualization against effects observed in cessation groups is crucial to evaluate validity and biological relevance.

The same shortcomings observed in BoE studies are often found in BoPH studies but are often accentuated due to the non-specific nature of the biomarkers, leading to smaller effect sizes, i.e. requiring larger sample sizes. Other important factors to consider when designing these types of studies is to ensure their time frame is long enough for assessment of biomarker reversibility, as many BoPHs may take months to reveal significant changes.

Few BoPH studies have been done in EC users, and most are cross-sectional and compare self-reported vapers with smokers. No standard panel of BoPHs has been established, but most studies focus on end points related to cancer, cardiovascular disease, the respiratory system, oxidative stress, and inflammation.

Spirometry measurements of lung function, like forced expiratory volume in 1 s (FEV₁) and forced vital capacity (FVC), have been used as surrogate end points for COPD. Most studies comparing FEV₁, FVC, or ratio of FEV₁ to FVC in healthy vapers and smokers have shown no significant differences (229-231). CIBELLA et al. (229) did, however, report significant increases of forced expiratory flow at 25-75% of FVC as well as fractional exhaled nitric oxide. D’RUIZ et al. (232) observed some significant changes for FEV₁ and FVC 5 days after smokers switched to an EC in a clinical setting, but, unexpectedly, saw no change in the cessation group.

For cancer, besides BoEs like NNAL and volatile organic compounds, studies overwhelmingly present lower levels of BoPHs in vapers than in smokers but higher than in cessation groups. Other BoPHs, such as the inflammation biomaker 8-epi-prostaglandin F₂α, have also been associated with lung cancer (233), and levels are significantly lower in exclusive vapers than in smokers (234). Similarly, a cross-sectional study by SONG et al. (235) concluded that most inflammatory BoPHs and cytokine concentrations in EC users were intermediate between those of smokers and non-smokers. In contrast, levels of 8-hydroxy-2′-deoxyguanosine, a biomarker for oxidative stress (236), have been reported to be higher in EC users than in non-smokers and not different to those in smokers (222).

Improvements in vascular health markers have been reported in smokers who switched to ECs for 1 month, particularly among women (237). Various BoPHs, such as 8-isoprostane (238) and 11-dehydro-thromboxane B₂ (239), have been associated with cardiovascular disease. Differences have been reported between smokers and vapers for 11-dehydro-thromboxane B₂ (234) but not for 8-isoprostane (222). Some reports have pointed to EC use as a potential cause of endothelial dysfunction (240) and heart rate variability (241, 242). In the PATH study, the association between vaping and heart failure was investigated, and the researchers concluded that respondents suffering heart failure had higher odds of being dual users than exclusive EC users (243). A comparison of vapers and/or dual users’ odds of suffering heart failure against those in smokers or never smokers would be of interest.

Most clinical studies assessing ECs have been small and with designs that limit interpretation and generalizability of conclusions. Studies should include appropriate controls, such as a cessation group (including people using NRT), as recommended by the Institute of Medicine (11), to provide context and determine the relevance of changes in relation to the time frame of the study. Much larger and longer-term studies assessing real-world behaviours are needed to fully understand the effects of switching to ECs, as the changes to health might take much longer to manifest than those traceable by other biomarkers in the short term (244).

4.3.4 Dual use

Whether dual use of combustible cigarettes and ECs provides beneficial changes to the harmful effects of smoking remains unclear. For instance, 5 days after switching half of cigarette consumption to ECs, slight decreases (7-38%) were seen in eight of nine urinary BoE, but concentrations of nicotine equivalents increased by 1-20% (245). In a 7-day switching study, only small reductions in BoEs were found in dual users, with much more substantial reductions seen in exclusive vapers or non-users of any tobacco product (214). In long-term dual users, SHAHAB et al. (221) found a similar pattern of increased concentrations of nicotine and nicotine equivalent, with little to no reduction in biomarkers of exposure. In contrast, a large study in long-term users by GONIE-WICZ et al. (219), in which average cigarette consumption in a dual use group was 15.1 and in a smoking group was 15.4, found BoEs in the group of dual users to be higher than in exclusive smokers, with NNAL on average 23% higher in dual users. However, this study showed a dose-response relationship, with BoE levels being significantly higher in dual users who smoked daily than in those who smoked occasionally, independently of whether they vaped occasionally or daily.

4.3.5 Pregnancy and reproductive toxicology

Animal studies have suggested that nicotine has potential teratogenic effects, although the evidence for harmful effects on fetal development and birth outcomes in humans
remains unclear (246). NRT is recommended for consideration in pregnant women who have been unable to quit smoking by behavioural changes (247, 248), but increased metabolism of nicotine during pregnancy might affect adherence to nicotine therapy (246, 249, 250). The relative risks of vaping during pregnancy are untested in randomised trials (246), and most data are descriptive and derived from surveys.

Physicians are an important source of information about the risks of nicotine and pregnancy, and women are likely to view them as being able to provide similarly reliable information about vaping. However, without objective data and with developments in devices likely outstripping published evidence, providing objective advice can be difficult (251). Women who use ECs while pregnant seem most commonly to believe that they are less harmful to mothers and babies than combustible cigarettes (although not completely harmless) and that use will help with quitting smoking (26, 252, 253). However, social stigma is viewed as a barrier to EC use in public (252).

Some argue that as the toxicology of ECs is similar to that of NRT (223, 254) it is likely to be a safer alternative to smoking in pregnant women. However, the amount of nicotine consumed via ECs could be as high as that consumed via combustible cigarettes (139, 207, 208, 255) and higher than received from NRT products and dose-effect data are unavailable.

Much more formal and standardised research is needed in this area, particularly on the safety of different nicotine levels, the risks of nicotine dependence among pregnant women who want to quit smoking but have been unable to, and adherence to prevent a return to smoking.

4.3.6 Mental health

Smoking prevalence is higher among people with mental health illnesses and conditions than in the general population, particularly those with severe mental illness or distress (256, 257). Rates of ever having tried vaping also seem to be higher (258), particularly among people with schizoaffective disorders and bipolar disorder (26). Among smokers with severe mental illness, strong associations were found with EC use, education level, and wish to quit smoking (quit attempt in the previous 6 months) (259).

Misconceptions among health professionals that smokers with severe mental illness are either not willing to quit or will suffer worsening symptoms as a result of doing so is hindering provision of adequate quitting options (260, 261). As well as NRT and supportive behavioural counselling, ASH (262) suggests that ECs could be considered for this subgroup of the population.

Formal studies are needed in this area to clarify the role that ECs could play in tobacco harm reduction.

4.3.7 Oral health

Tobacco consumption is associated with oral diseases (263), but whether ECs lessen or contribute to the burden is unclear. A study investigating numerous end points (plaque index, bleeding on probing, probing depth, clinical attachment loss, number of missing teeth, and gingival crevicular fluid levels of pro-inflammatory cytokine) found consistent significant differences between smokers and never-smokers, whereas there was no difference between the vapers and never smokers (264). However, in a pilot study, some biomarkers associated with antimicrobial activity and inflammation were increased in EC users compared with in never smokers (265). The findings from these two studies appear to synthesize the conclusion from a systematic review, in which 99 publications investigating ECs and oral health (mouth, throat, periodontal, dental, cytotoxic/genotoxic/oncological, oral microbiome, and traumatic/accidental injury) were assessed (266). Cosmetically, ECs lead to less tooth enamel staining than cigarette smoke. This difference might have social benefits to former smokers who have switched to ECs (267, 268).

Overall, the evidence suggested that while switching from smoking to ECs mitigates some smoking-induced symptoms, a wide range of oral issues could be associated with vaping. However, most of the evidence in the area is weak, with studies so far not specifically designed to assess oral health outcomes.

5. PERCEPTIONS AND BEHAVIOURS - USER DEMOGRAPHICS

Perception of risks associated with ECs can be an important determinant of product use (269). Misconceptions about the harmfullness of ECs versus combustible cigarettes seems to be a growing reason among smokers to reject them (38, 59). In this section we review studies investigating perceptions about ECs and nicotine use behaviours associated with those perceptions.

5.1 Consumer perception studies

A survey conducted in six European countries suggested that among respondents who were aware of ECs in 2016, 58.5% perceived them to be as risky or of higher risk than cigarettes, increasing to 61.8% in 2018 (270). Only around a quarter of respondents perceived reduced risk with ECs (28.6% and 28.4% in 2016 and 2018, respectively). A similar increasing trend in perceived high risk of ECs was seen in a US survey, where 11.5% (95% CI 10.0-13.2%) of adults viewed them to be as harmful as smoking in 2012 but 36.4% (35.1-37.7%) did so in 2017 (271). The importance of risk perception amongst vapers is clear, as shown in another study where dual users who perceived ECs as being less harmful than smoking were more likely to be exclusive vapers after 1 year than those who did not perceive them as less harmful (7.5% vs 2.7%, adjusted odds ratio 2.9, 95% CI 1.7-4.8) (269). It is worth noting that, according to an analysis based on the PATH study, the proportion of US adults perceiving e-cigarettes as harmful or more than cigarettes steadily increased from 53.7% to 72.7% between 2014 and 2016 (272). Other perceptions, such as product addictiveness, social acceptability, potential to harm others, and environmental impact, may also affect product choice. The most common reasons to use ECs among adults and youth in one survey were smoking cessation and novelty, respectively (273). In another study, the two main reasons for using ECs by current and former smokers were perceptions that they could be helpful to quit
and were less harmful than smoking (274). In a European wide survey in 2014, the main reasons given for use of ECs were to stop or reduce smoking and being able to use them in places where smoking was banned (275), while in 2020, reducing tobacco consumption was still the main reason for using ECs followed by believing they were less harmful than cigarettes (14). In the UK, ASH (276) reported that the three main reasons for vaping were as an aid to quit smoking, remain abstinent from smoking, and save money.

5.2 Switching to ECs and abuse liability

One criticism of ECs is their inefficacy for sustaining exclusive vaping and propensity to facilitate dual usage (277). These views, in part at least, were based on early studies of products providing low nicotine delivery and hence low user satisfaction (278). While ECs are not marketed as smoking cessation products, a large 1-year study in the UK showed that the smoking abstinence rate among people who switched to later-generation ECs was roughly double that among those who switched completely to NRT (212).

For smokers attempting to quit smoking, higher reward from ECs could help them to completely transition away from combustible cigarettes, as frequency of use of vaping products has been positively associated with becoming a former smoker with quit durations of 2-6 years (188, 279). However, increases in nicotine exposure could raise concerns about the abuse liability of ECs. Abuse liability is the likelihood of engaging in persistent and problematic use of a substance that will lead to undesirable consequences (280). High nicotine delivery via ECs could increase the risk of abuse liability. However, if ECs can provide a viable alternative to cigarettes, they might have a public health benefit (24, 281, 282) and some degree of abuse liability might be acceptable (283, 284). A standard methodology has been established to assess the abuse liability of pharmaceuticals (285) and is largely adaptable for tobacco products (280, 286). This type of study is likely to be most relevant in countries where high concentrations of nicotine are allowed in e-liquids, such as the USA (287).

In a prospective direct comparison of ECs with smoking and NRT (nicotine gum), STILES et al. (96) found that while their study showed ECs probably had some degree of abuse liability, it was much closer to that of NRT than to combustible cigarettes. This conclusion was reinforced at category level by the analyses of symptoms of dependence collected through national US surveys, the Population Assessment of Tobacco and Health (PATH) (288, 289) and the National Adult Tobacco Survey (290). Both identified dependence symptoms in EC users but to a substantially lesser degree than in smokers. Another retrospective study, based on the International Tobacco Control database, investigated differences in symptoms of dependence between vaping and non-vaping ex-smokers in four countries (USA, UK, Australia, and Canada) (291). Vapers were more likely to perceive themselves as very addicted to smoking, but at the same time to feel more confident about remaining abstinent from smoking and to experience fewer urges to smoke than non-vapers.

5.3 Vapers demographics - uptake by young people and potential gateway effects

Vaping products have experienced an increase in popularity all around the World. In Europe estimated vaping prevalence increased from 1.5% in 2014 to 1.8% in 2017 (292). Ever use ranged widely from 5.5% to 56.5% and was highest in younger age groups, with studies reporting consumption from respondents ranging from 10-24 years old. In the USA a larger study with 158,626 participants (293) reported ever use of vaping products of 14.8%, 12.8%, 9.4%, 7.0%, 2.3% in the age groups 18-24, 25-34, 35-44, 45-64, ≥65 years, respectively, while regular use (in ≥20 of the previous 30 days) was more comparable across the same age groups (1.3%, 1.3%, 1.2%, 1.0%, 0.4%, respectively). In the UK, where uptake of ECs has been high, ever use in 2019 was estimated to be 16.5%, 20.1%, 12.3%, 10.8%, 5.2% in the age groups 16-24, 25-34, 35-49, 50-59, ≥60 years and 3.3%, 9.2%, 7.3%, 7.1%, 3.0%, respectively were regular users (294). Prevalence of vaping is generally lower among women than men, as for smoking (292, 295). Most vapers smoke or have smoked in the past. Vapers without smoking history account for a very small proportion of all vapers (26, 292, 294, 296-298).

Youth EC initiation has taken centre stage in the EC scientific world since the US Surgeon General declared EC use among youth “an epidemic” (299). Public Health England’s (PHE) annual review estimated that EC prevalence with use of once per week or less was around 5% among 11-18-year olds, but varied by age. Prevalence among 11-year olds was 1% up to 5% among 15 year olds (26). A large 2017 review of surveys involving 60,000 children aged 11-16 years in the UK suggested that the prevalence of more frequent regular use (at least weekly) was 3%, even though proportions of 7-18% had ever tried ECs (300). Most young people regularly using ECs were already smokers, and among never smokers, only 0.1-0.5% regularly used ECs. In the US, uptake seems to be higher, with 13.1% of middle-school and high-school students nationally reported to be current EC users in 2015-2017, although most users (76.7%) also used at least one other tobacco product (301). However, smoking initiation rates among youth in the US reached the lowest recorded rate of 2.29% in 2018 (302), and similar patterns have been observed across European countries where ECs are widely available (303). Friend or caregiver smoking seems to increase the likelihood of children trying ECs, as does lower socioeconomic status (304, 305). Differing perceptions of risks have been found across subgroups of young people (e.g., classified by ethnic origin or sexuality) (306), but little work has been done on social factors (307), and this area needs greater attention.

Gateway theory originates in the use of a psychoactive drug being viewed as increasing the likelihood of using further drugs. When applied to vaping, it describes changes in a biological and/or behavioural pathway seen with use of a lower-risk product, such as an EC, increasing the risk of smoking combustible cigarettes for a higher reward (308). This theory has been cited to support the banning or restriction of access to EC products and liquids containing nicotine, for instance in Australia (309), but it is not backed
up by reliable evidence (29, 310, 311). Application of such policies risk denying adult smokers the opportunity to switch to ECs and might increase relapse to smoking or smoking initiation (312). Kasza et al. (313) analysed the US PATH study database from 2013 to 2016 and found that ever users of ECs aged 12-17 years were more likely to have smoked in the previous 30 days at follow-up (adjusted odds ratio 3.4, 95% CI 2.4-4.7%). However, the likelihood of smoking was increased by use of any other tobacco product, including hookahs and smokeless tobacco. EC use was similarly increased by smoking (adjusted odds ratio 2.9, 95% CI 2.1-4.0%). Thus, changing to smoking could be explained by youth experimentation and propensity to risk (314, 315). Concurrent use of nicotine products has also been reported by AUF et al. (316). However, national surveys do not suggest any gateway effect. Studies from the USA (288, 302, 317), UK, New Zealand (318) and Canada (319), have concluded that (i) smoking usually precedes vaping; (ii) regular vaping is rare amongst never smokers; (iii) not all adolescent vapers used nicotine and dependence was lower than for smokers; (iv) since vaping has been introduced, smoking rates have continued to decline. The Canadian study concluded, “when it comes to smoking cigarettes, very few smoked cigarettes in addition to vaping and fewer still believe they started smoking after they had started vaping” (319).

5.4. Use behaviour studies

Consumer use behaviour studies can provide an understanding of puffing topography, potential nicotine uptake, and variability in patterns of usage between different EC types and users (37, 320). The data are crucial for understanding how consumers use products and play a key part in setting the scientific framework for assessing risk potential. EC use differs significantly from cigarette smoking, although more information is needed on topography, perceptions, and behaviours. The US FDA recommends conducting “actual use” studies in “real-world conditions” within their Modified Risk Tobacco Product Application guidelines (73). Consumer use behaviour studies should adhere to the principles of good clinical research practice, which aim to protect the wellbeing of participants and ensure appropriate study execution and data traceability. Attempts are being made to establish independent ethics committees that can weigh risks against (participant and society) benefits of use behaviour studies conducted with consumer products. Such committees would ensure that the rights, safety, and wellbeing of trial participants prevail over the interests of researchers, science, and society by providing participants with adequate information on study products; details of the study in a scientifically sound protocol; obtaining informed consent from every participant prior to participation; ensuring that the data generated are stored, recorded, handled, and accurately interpreted, verified, and reported by implementing quality systems and procedures.

In a typical EC use behaviour study, volunteers who have given informed consent are trained in the use of the products necessary to ensure familiarity and are provided with the test product for use at home over a fixed period. Consumption patterns at home are self-reported while periodic attendance at a study site might also be required to assess puffing behaviour with a topography device (320, 321). Questionnaires might be used to obtain feedback about the sensory experience of vaping, satisfaction with selected attributes, and overall acceptability (322). Results from typical topography studies have been summarised in Table 5.

Hammond et al. (323) concluded that ECs topography studies “show a high degree of stability in puffing behaviour within the same subject over time, but considerable variability between e-cigarette users”. Thus, more-granular information is needed to improve the accuracy of topography data and how they relate to nicotine exposure in users’ everyday environments. To enable the collection of real-life data over longer periods of time, attempts have been made to incorporate topography devices into ECs that record various attributes and transmit data via an internet-enabled electronic device to cloud data platforms (Table 6). Further work is needed to validate the accuracy and reliability of the data generated by these connected ECs compared to traditional instruments, but they seem not to substantially affect puffing behaviour (324).

Topography data can be used to improve understanding of baseline characteristics related to EC use, which can then be used to establish representative vaping machine protocols. While standardization of regimes would be valuable to industry, academics, and regulators, no single regime is likely to represent true human behaviour or produce emissions linked closely enough to human exposure given the wide range of puffing behaviours. CORESTA Recommended Method N° 81 lays out the essential requirements necessary to generate and collect EC aerosol for analytical testing purposes (112), but the parameters do not reflect intense use.

Rather than using maximum settings for intense regimes, parameters for puff duration, volume, frequency, profile, and number, battery charge status, coil or atomiser age, voltage setting, ventilation setting, and device orientation should be based on representative human usage data. These parameters are not all independent and improved understanding of how different combinations affect the amount of aerosol generated will be central to defining protocols for testing and regulating ECs.

6. BRIDGING STUDIES

Given the pace of EC innovation, providing the amount of data required for regulatory decisions while a product remains relevant is not always possible. Borrowed from the pharmaceutical industry, the concept of bridging applies the best practice data from an existing product to the design of a similar product and updates only data pertinent to modifications (95). For example, for ‘biosimilars’ in Europe, data from a reference drug are supplied and the only new data are those which show that the new variant does not diverge in safety or efficacy from the reference (325). In ECs this can be translated to maintaining product safety while ensuring the new variant does not increase health risks to users and non-users. Regulatory bodies, such as the FDA, recognize the potential of this approach for ECs as long as it is supported by a rationale and justification (66).
<table>
<thead>
<tr>
<th>Reference</th>
<th>Electronic cigarette type</th>
<th>Mode of activation</th>
<th>Topography device</th>
<th>Mean (± SD) puff characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of pieces</td>
<td>Components</td>
<td>Rechargeable device</td>
<td>Refillable cartridge</td>
</tr>
<tr>
<td>BEHAR et al., 2015 (359)</td>
<td>1</td>
<td>All-in-one</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CUNNINGHAM et al., 2016 (320)</td>
<td>1</td>
<td>All-in-one</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>NORTON et al., 2014 (360)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>LEE et al., 2015 (361)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>BEHAR et al., 2015 (359)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CUNNINGHAM et al., 2016 (320)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>JONES et al., 2020 (322)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Table 6. Connected e-cigarette-based ad libitum topography measurement of various e-cigarette types.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Electronic cigarette type</th>
<th>Mode of activation</th>
<th>Topography device</th>
<th>Mean (± SD) puff characteristics</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No. of pieces</td>
<td>Components</td>
<td>Rechargeable device</td>
<td>Refillable cartridge</td>
</tr>
<tr>
<td>ROBINSON et al., 2015 (362)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>ROBINSON et al., 2016 (363)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>DAWKINS et al., 2016 (364)</td>
<td>3</td>
<td>Battery, cartridge &amp; atomizer</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>FARSALINOS et al., 2018 (344)</td>
<td>3</td>
<td>Battery, cartridge &amp; atomizer</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>LEE et al., 2018 (365)</td>
<td>2</td>
<td>Battery &amp; cartomizer</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
Thus, for an EC variant of an existing product, if the changes do not affect factors like age, gender, race of users or cultural environmental factors, data could be reused from studies using earlier models of the product and new bridging data should be only required only for those aspects which could potentially be affected by the changes.

7. POPULATION MODELLING

Modelling has become important to support risk-benefit assessments and policy decisions in tobacco control because it provides projections based on credible simplifications of complex mechanisms underlying nicotine use. The strength of modelling resides in the capability of processing many parameters with complex interactions rather than looking at one aspect of an issue at a time. Additionally, the impact of inputs’ uncertainty may be assessed. A wide range of topics in relation to tobacco control and harm reduction has been assessed, from the impact of taxation of cigarettes (326) to banning menthol cigarettes in the USA (327). In assessment of potential health benefits or burdens from commercialization of ECs, models have been used to consider morbidity or mortality at the population level, including EC use versus smoking in adults and youth, possible effects of different proportions of dual use, and complete displacement of cigarettes by ECs.

There are two main types of nicotine population models. First, microsimulation models aggregate changes at the individual level (328). Various parameters can be set to reflect individual characteristics and interactions between the units (people). Macrosimulations involve groups of people considered to be homogenous individuals with respect to the main factors affecting the outcome (329). Macrosimulations can be further separated into two main categories: birth cohort models (330) and system models (331). In birth cohort models, a group of homogenous individuals born in a specific year (e.g., smokers born in 1960) is followed up until death or a timepoint. The potential impact of introducing different scenarios involving ECs is projected, and effects are compared to the counterfactual scenario of no change (i.e., the status quo is projected, and effects are compared to the potential impact of introducing different scenarios involving ECs.

Beyond the USA, HILL and CAMACHO (338) used a system model to estimate differences in effects from 2000 to 2050 between the introduction and no introduction of ECs in the UK. It was assumed that there would be no reduction in risk for dual users and any benefit gained by switching would be lost for people who relapsed to smoking. The model still suggested a beneficial impact from introducing ECs, with smoking-related deaths in 2050 projected to fall to 8.4% in the status quo scenario compared with 8.1% in the vaping scenario, and to 11.2% versus 10.5% in people younger than 75 years.

A model used by BACHAND et al. (335) suggested that if only 2% of smokers switched completely to a lower-risk product in all age-groups, population survival would be significantly enhanced by 3.127 lives. Survival would increase with the growing proportion of complete switchers. The gain would also offset unintended exposure patterns, such as use of lower-risk products leading to cigarette smoking initiation by never users or dual use by smokers. Credibility of these outcomes were reinforced by CHERING et al. (336), who concluded that simulated effects of ECs on smoking cessation would generate substantially greater decreases in smoking prevalence than increases in smoking initiation.

Not all model projections based on US data have been favourable to ECs. SONEJI et al. (337) projected between 1.3 and 1.15 million life-years lost by introducing ECs. This opposition in directionality to most of the other modelling efforts could be due to over-pessimistic inputs with high gateway effects into smoking from vaping and low quitting rates from smoking to vaping. This study highlights the importance of using not only possible but credible inputs based on robust scientific data.

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<table>
<thead>
<tr>
<th>Reference</th>
<th>Focus and assumptions</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEVY et al., 2018 (334)</td>
<td>Status quo scenario developed to project smoking rates and health outcomes in the absence of vaping, compared with substitution models in which combustible cigarette use is largely replaced by vaping over a 10-year period</td>
<td>Projections show that a strategy of replacing cigarette smoking with vaping would yield substantial life-year gains, even under pessimistic assumptions regarding cessation, initiation and relative harm</td>
</tr>
<tr>
<td>LEVY et al., 2017 (366)</td>
<td>Alteration in smoking patterns caused by transitions from trial of e-cigarettes to established vaping (exclusive or dual use) and effects of cessation at later ages in a 1997 birth cohort; measured by estimated public health impact on deaths and life-years lost incorporating evidence-informed parameter estimates</td>
<td>Conservative assumptions indicated reductions of 21% in smoking-attributable deaths and of 20% in life-years lost with established vaping compared to no vaping. Health gains from vaping were especially sensitive to vaping risks and use rates among those who were otherwise likely to smoke cigarettes</td>
</tr>
<tr>
<td>LEVY et al., 2019 (367)</td>
<td>Cohort-specific simulation model of the impact of e-cigarettes containing nicotine on smoking cessation by adult smokers and premature deaths and life-years lost, by gender in two US birth cohorts aged 30 or 50 years in 2012</td>
<td>Vaping was projected to have a net positive impact on population health over a wide range of plausible levels of use (transitions to dual, exclusive, and no e-cigarette use) and vaping risks, although net impact was sensitive to parameter estimates</td>
</tr>
<tr>
<td>WARNER &amp; MENDEZ, 2019 (333)</td>
<td>Dynamic model that tracked smoking status in the US adult population and smoking-related deaths over time and the effects of vaping-induced smoking initiation and cessation on life-years saved or lost to the year 2070</td>
<td>Health benefits were strongly suggested for e-cigarette use, in terms of their potential to increase adult smoking cessation, that exceeded risks to health resulting from increasing the number of youthful smoking initiators</td>
</tr>
<tr>
<td>PETROVIĆ-VAN DER DEEN et al., 2019 (368)</td>
<td>Multistate life-table model of 16 tobacco-related diseases that simulated lifetime quality-adjusted life-years and health-system costs at a 0% discount rate, incorporating transitions from never, former, and current smoker states to and from regular vaping and based on literature estimates for relative risk of disease incidence for vaping vs. smoking</td>
<td>A regulatory environment permissive of vaping achieved net health-gain and cost savings, although uncertainty intervals were wide</td>
</tr>
<tr>
<td>CHERNG et al., 2016 (336)</td>
<td>Agent-based model examining hypothetical scenarios of e-cigarette use by smoking status and e-cigarette effects on smoking initiation and smoking cessation</td>
<td>With current patterns of e-cigarette use by smoking status and the heavy concentration of e-cigarette use among current smokers, simulated effects of e-cigarettes on smoking cessation generated substantially larger changes to smoking prevalence than on smoking initiation</td>
</tr>
<tr>
<td>SONEJI et al., 2018 (337)</td>
<td>Monte Carlo stochastic simulation model of expected years of life gained or lost due to effects of e-cigarette use on smoking cessation among current smokers and transition to long-term cigarette smoking among never smokers in 2014 US population, with model parameters drawn from census counts, national health and tobacco use surveys, and published literature</td>
<td>The existing evidence and optimistic assumptions about the relative harm of e-cigarette use compared to cigarette smoking, suggest that e-cigarette use currently represents more population-level harm than benefit</td>
</tr>
<tr>
<td>KALKHORAN &amp; GLANTZ, 2015 (369)</td>
<td>A base case model using data on reported cigarette and e-cigarette use patterns in the US and UK to quantify transitions from no cigarette or e-cigarette use to never use of either, cigarette use, e-cigarette use, dual use, or quit</td>
<td>If e-cigarette use increased only among smokers interested in quitting vs more quit attempts and no increased initiation of e-cigarette use among non-smokers or e-cigarettes were taken up only by youth who would have smoked conventional cigarettes, population-level health benefits were estimated regardless of e-cigarette health costs. Conversely, scenarios in which e-cigarette promotion led to renormalisation of cigarette smoking or ECs were used primarily by youth who never would have smoked, net health harms were estimated across all e-cigarette health costs. In other scenarios, the net health effects varied by the health costs of e-cigarettes</td>
</tr>
<tr>
<td>HILL &amp; CAMACHO, 2017 (338)</td>
<td>System Dynamics Model representing UK population. Assumes the risk of dual users is the same as smokers and any benefit obtained from quitting is lost if there is a relapse to smoking. Provide projections to 2050.</td>
<td>The results suggest that by 2050, smoking prevalence in adults could be as low as 12.4% in the core model and 9.7% (including dual users) in the counterfactual. Smoking-related mortality would be 8.4% and 8.1%, respectively.</td>
</tr>
</tbody>
</table>
In summary, a wide range of models have been used to assess the potential impact of commercialization of ECs and, when credible inputs are considered, these models have pointed to an overall health benefit at the population level.

8. DISCUSSION

Despite extensive variation in EC devices and e-liquid formulations (106), in the absence of tobacco combustion, EC aerosol is much simpler than cigarette smoke and the numbers and concentrations of compounds present are substantially lower (19-22). To promote comparability and interpretability, testing of ECs should be performed using appropriate puffing parameters (42, 75-78, 112) and always with the measurement of air blanks to contextualize contamination by laboratory-based toxicants (20).

Frequently, flavouring ingredients are not fully listed on packaging. To maximize safety, manufacturers should restrict flavours to ingredients that are food grade or generally recognized as safe (339), and perform appropriate testing when the toxicological profile is not well characterized (87). Of note, many ingredients have not been tested for safety when consumed by aerosolization and inhalation and/or when heated, and effects might not transfer reliably from ingestion. For example, diacetyl, which gives a butterscotch flavour, is safe to eat but when inhaled in large amounts in popcorn factories was associated with bronchiolitis obliterans, also known as popcorn lung. As a result, this flavouring is banned in ECs in many countries, although testing at the very low levels that would be required has not been performed (93). Such safety aspects of EC design and ingredients continue to evolve through manufacturers product stewardship, and are being reflected in regulatory guidance (106). A wide range of assessment methods, including toxicological assays (88), three-dimensional organotypic models (161, 169, 181), and in silico risk assessments (47) can be useful to guide product design and standards. The consolidation and standardization of methods and endorsements of testing frameworks by regulators will be important next steps to increase product quality within the EC category.

The gold standard to investigate EC-associated health risks are clinical and epidemiological studies. However, clinical studies are expensive and, therefore, primarily conducted through sponsorship by large manufacturers, which could bias studies towards well-designed and highly stewarded products. While epidemiological outcomes can be difficult to unravel, it as might take many years to observe significant changes, reversibility of harm from smoking as well as epidemiological effects might be further complicated by the fluidity between products among nicotine users. For exposure to toxicants, reduced levels of BoEs in exclusive vapers have been confirmed at population level, even with heterogeneity in products and how they are used (219), and BoPH and biomarkers of biological effect studies suggest a reduction of risk of acute health effects caused by smoking (340). Further work is required, particularly on endothelial dysfunction, oxidative stress, and cancer.

In conclusion, the harm reduction potential of ECs will be maximized by complete displacement of cigarettes. Two aspects will have a critical impact on the effectiveness of ECs to displace smoking.

- First will be the manufacture of robust, high-quality products that compete with conventional cigarettes by satisfying consumers through product performance, sensorial characteristics, and nicotine delivery, while striking a balance against abuse liability. Manufacturers must use these and all other tools they have, including flavours, to make ECs a more attractive proposition to adults than smoking.
- Second, public health institutions must unambiguously and accurately inform smokers about the likely reduced risk character of ECs compared with cigarettes. The UK has seen some public health institutions openly supporting ECs as lower risk alternatives to smoking. In 2019, more than 50% of all vapers in the UK used ECs exclusively (294) and smoking prevalence reached a record minimum of 15.8%, down from 16.6% in 2018 (341). Consolidating this trend, the proportion of former smokers in 2019 was the highest recorded at 62.5% (341).

Despite all evidence supporting ECs as reduced risk products as part of a smoking harm reduction framework, outright bans and restrictions of ECs or flavoured e-liquids continue in many countries, and others are introducing restrictions, for example on flavours, that are not supported by scientific evidence. The main reasons being used to ban or legislate against ECs are underage usage and the hypothesised gateway effect. However, irresponsible marketing of vaping products has led to a situation of distrust between governments and the vaping industry and is an area that needs to be addressed. As this topic is highly controversial, it may deviate from the scientific focus of this review. It is mentioned as it clearly can have an impact on initiation, but it deserves a publication of its own.

At population level, national surveys do not suggest any gateway effect, and smoking initiation rates among youth in the US also indicate the absence of such an effect and the lowest rates of smoking initiation on record in 2018 (2.29%) (302). Similar patterns have been observed across European countries where ECs are widely available (303) and are also suggested by a study commissioned by HEALTH CANADA (319). Regulation of all aspects limiting the efficacy of ECs as an alternative to smoking should be considered with caution, as such measures could reduce the attractiveness of ECs for smokers and reignite smoking initiation (312).

9. CONCLUSIONS

- Regulatory strategies must promote quality in product development led by robust stewardship which is essential to identify and eliminate, or minimize potential hazards.
- Vapour products have been soundly demonstrated to be able to reduce exposure to toxicants found in conventional cigarette smoke among smokers who transition completely to vapour products.
- Emerging evidence in biomarkers of effect point to lower risk for most smoking-related disease endpoints, with further research required particularly for cardio-
vascular endpoints, where there are conflicting data.  
- Vapour products must offer a compelling alternative to smoking to attract smokers, including flavours while mitigating products' youth appeal  
- Research suggests lower abuse liability from vaping products in comparison with conventional cigarettes  
- Gateway effect claims are generally not sustained by public data which show lowest levels of smoking initiation ever recorded in key markets such as the US and UK.

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REFERENCES


49. Kim, H., J. Lim, S.S. Buehler, M.C. Brinkman, N.M. Johnson, L. Wilson, K.S. Cross, and P.I. Clark: Role of Sweet and Other Flavours in Liking and Disliking of Electronic Cigarettes; Tob. Control 25 (2016) ii55-ii61. DOI: 10.1136/tobaccocontrol-2016-053221


57. Audrain-McGovern, J., A.A. Strasser, and E.P. Wileyto: The Impact of Flavoring on the Rewarding and Reinforcing Value of E-Cigarettes with Nicotine Among Young Adult Smokers; Drug Alcohol Depend. 166 (2016) 263-267. DOI: 10.1016/j.drugalcdep.2016.06.030


102. Tayyarah, R. and G.A. Long: Comparison of Select Analytes in Aerosol from E-Cigarettes with Smoke from Conventional Cigarettes and with Ambient Air; Regul. Toxicol. Pharmacol. 70 (2014) 704-710. DOI: 10.1016/j.yrtph.2014.10.010


126. Williams, M., K.N. Bozhilov, and P. Talbot: Analysis of the Elements and Metals in Multiple Generations of Electronic Cigarette Atomizers; Environ. Res. 175 (2019) 156-166. DOI: 10.1016/j.envres.2019.05.014


130. Zhao, D., A. Navas-Acien, V. Ilievski, V. Slavkovich, P.


197. Digard, H., C. Proctor, A. Kulasekaran, U. Malmqvist,


102

873-878. DOI: 10.1158/1940-6207.CAPR-15-0058
234. Oliveri, D., Q. Liang, and M. Sarkar: Real-World Evidence of Differences in Biomarkers of Exposure to Select Harmful and Potentially Harmful Constituents and Biomarkers of Potential Harm Between Adult E-Vapor Users and Adult Cigarette Smokers; Nicotine Tob. Res. 22 (2020) 1114-1122. DOI: 10.1093/nttr/ntz185
DOI: 10.1007/978-94-007-7741-5_31-1

DOI: 10.1016/j.prostaglandins.2017.11.003

DOI: 10.1093/eurheartj/ehz772

DOI: 10.1097/HJH.0000000000001890

DOI: 10.1161/JAHA.117.006579

DOI: 10.1016/j.hrtlng.2019.11.006

DOI: 10.26355/eurrev_201901_16789

DOI: 10.1080/15376516.2016.1196282

DOI: 10.1002/14651858.CD010078.pub3


DOI: 10.1136/bmj.g1622

DOI: 10.1111/add.13029

DOI: 10.1016/j.pmedr.2017.07.012

DOI: 10.1186/s12884-018-1856-4

DOI: 10.1093/her/cyw059

DOI: 10.1093/nttrx/ntx258

DOI: 10.1097/OGX.0000000000000595

DOI: 10.1146/annurev-publhealth-031816-044618

DOI: 10.26355/eurrev_201901_16789

DOI: 10.1016/j.pmedr.2017.07.012

259. Peckham, E., M. Misha, C. Fairhurst, D. Robson, T. Bradshaw, C. Arundel, D. Bailey, P. Heron, S. Ker, and S. Gibboly: E-Cigarette Use and Associated Factors.
Among Smokers with Severe Mental Illness; Addict. Behav. 108 (2020) 106456. DOI: 10.1016/j.addbeh.2020.106456


279. Farsalinos, K.E. and R. Niaura: E-Cigarettes and Smoking Cessation Among Smokers with Severe Mental Illness; Addict. Behav. 30 (2005) 1283. DOI: 10.1016/j.addbeh.2004.08.050


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