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REVIEW

Nicotine in electronic cigarettes

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Abstract
Electronic cigarettes (ECs) are battery-powered gadgets that heat liquid to produce an aerosol. Nicotine is a primary ingredient in some e-liquids; however, due to a lack of quality control regulations, the nicotine may become tainted, or the measured and labelled values may not correspond. To avoid such issues, it is essential to identify the components that contribute to erroneous nicotine quantification. Herein, the differences between free-base nicotine and nicotine salts are discussed, highlighting the lower volatility of nicotine salts and their longer persistence in the body. Discrepancies were noted in the concentration of nicotine salts in some e-liquid samples, with labelled and measured values of 48 and 68.8 mg/mL, respectively, in one sample, and 24 and 33.1 mg/mL, respectively, in another. Inconsistencies were also observed in e-liquids labelled as nicotine-free: one sample had a nicotine concentration of 21.80 mg/cartridge, while another had a concentration of 23.91 mg/mL. The review also covers differences in the potency, flavour, and storage of nicotine under various conditions. Additionally, the literature suggests that the components in ECs are separated into the liquid and vapour phases; thus, phase selection should be considered to ensure optimal experimental outcomes. For instance, the vapour phase comprises the greatest quantities of volatile organic compounds, even though nicotine has been detected in all phases. Finally, the role of ECs in smoking cessation is discussed. The reviewed findings underscore the need for further research on e-liquids, particularly regarding their long-term clinical effects.

Keywords Nicotine · Humectant · Flavouring · Propylene glycol (PG) · Aerosol

1 Introduction

The first patent for electronic cigarettes (ECs) was filed in the 1930s for storing and heating medicines. In 1965, ECs were recognised as a healthy alternative to inhaling nicotine [1], with Gilbert referring to them as cigarettes without smoke or tobacco [2, 3]. Later, in 2003, the pharmacist Hon Lik developed the first generation of modern ECs following the death of his father from lung cancer [1, 3]. According to the literature, the components of ECs were first analysed in 2004 [4], and in 2008, Health New Zealand investigated electronic liquid (e-liquid) components present in both the liquid and aerosol phases of ECs [5].

While ECs are designed to resemble normal cigarettes (NCs) in appearance [6], unlike NCs, they contain a battery-activated heating element (atomiser) to convert e-liquid (contained in a cartridge) into an aerosol that the user can inhale [7, 8]; the atomiser is activated by either pressing a button or drawing a breath through the mouthpiece [9, 10].

Recent advances have been made in the exterior design of ECs, which can comprise one or two (battery and cartomiser) pieces, or three pieces, where the cartridge and atomiser are separated [11]. Furthermore, the cartridge can be categorised as disposable or refillable [8, 9]. As specified by manufacturers, the temperature of the vaporisation chambers in ECs ranges from 40 to 65 °C [9], though no accurate data exists regarding the temperature range of modern devices [8, 9]. Several settings can be adjusted by the user, including the temperature, e-liquid flavour, and nicotine concentration [8, 12].

Because of the rapid introduction of ECs to the market [3, 13, 14], nomenclature has been developed to distinguish them from NCs. For example, using ECs is referred to as "vaping", and the user is referred to as a "vaper", while using NCs is termed "smoking", where the user is a "smoker" [8, 15, 16].

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The e-liquid used in ECs is an oily and highly viscous liquid [5, 17, 18], the components of which determine its colour and aroma [5, 19, 20]; numerous researchers have noted that e-liquids contain an array of compounds to generate flavour and aroma [5, 21–23]. Recent studies have investigated the discrepancy between the labelled and measured concentration values of e-liquid components [1, 24–26]. For example, the nicotine concentrations indicated on the labels of e-liquids differ from the measured values [7, 27–29]. Similarly, products labelled as "nicotine-free", indicating the absence of nicotine in the e-liquid, have been found to contain nicotine [5, 30]. Nicotine is a highly addictive substance extracted from tobacco and represents one of the key components of both the liquid and vapour phases of ECs [3, 5, 31, 32]. The degree of purity can vary according to both the manufacturer's protocol and the process of extraction, which may result in the presence of harmful impurities [5, 17, 31]. These impurities, comprising alkaloids, can arise from poor extraction, the oxidation of flavours from unstable formulations, exposure to high temperatures, or poor storage conditions [9, 33–35].

Nicotine concentrations in e-liquids range from 0 to 100 mg/mL, with the most common interval being 3–36 mg/mL [9, 36]. These levels contravene European Union guidelines, which specify that the maximum concentration of nicotine that e-liquids can contain is 20 mg/mL [37]. Furthermore, the lethal dose is 0.8–1 mg/kg of the body weight in non-smoking adults [5, 38, 39]. This has prompted scholars to extensively explore the importance of nicotine in ECs, especially the correspondence between measured and labelled nicotine contents.

There is a considerable gap in the literature regarding the stability of nicotine in e-liquids under different storage conditions and the effects of temperature and different flavour additives. In addition, the role of ECs in smoking cessation and the effects of different nicotine salt liquids have not been extensively studied. This dearth of studies is concerning given the wide range of nicotine-containing products available on the market.

This literature review mainly aims to provide a complete conceptual framework clarifying the differences in the types of nicotine, identifying the optimum instruments for estimating nicotine levels in the vapour and liquid phases, investigating the properties of nicotine and its stability during storage, and assessing the impact of different flavours and temperature changes. Subsequently, the differences between the labelled and measured concentration values of e-liquids are highlighted, with an exploration of their common and less common compounds. Finally, the review presents a discussion on whether ECs contribute to smokers quitting, helping to evaluate e-liquids in terms of their components, the quantity of nicotine and other compounds they contain, and their safety.

Data gathered between 2011 and 2023 were mainly considered in this review to generate the most up-to-date information. References were acquired by searching various databases, including CORE, Scopus, Web of Science, PubMed, and ScienceDirect; 129 references were used and 32 studies were compared, as summarised in figures and tables. For simplicity and to limit the topics considered, the first search involved identifying articles with the following keywords in their titles: "nicotine-free liquids", "nicotine salts", "volatile organic compounds (VOCs)", "flavours", "nicotine", and "e-liquids".

2 Different types of nicotine

Most e-liquids contain nicotine extracted from tobacco because synthetic nicotine is costly to produce [33, 40]. Nicotine is divided into three forms according to its protonation state—un-, mono-, and di-protonated nicotine—with the first two types being used in e-liquids [41]. The different types of nicotine have attracted interest due to their different absorption characteristics and sensory effects [42–44]. With the rapid growth of e-liquid products, nicotine has been classified into two categories: free-base nicotine (un-protonated) and nicotine salts (mono-protonated). In investigating the influence of pH on nicotine absorption, Wilhelm et al. noted that the concentration of nicotine increased as the pH increased, suggesting that free-base nicotine was more readily absorbed than salt nicotine [45]. On the other hand, a patent filed by Pax Labs (the company that produces Pax vaporisers) demonstrates that nicotine salts lead to higher nicotine concentrations in the plasma, suggesting that mono-protonated nicotine exhibits better absorption than the free-base form [44]. Given the significant debate over the different forms of nicotine in the scientific community, it is essential to distinguish between the two types and explain the nature of each.

2.1 Free-base nicotine

Free-base nicotine is also known as un-protonated nicotine since it lacks a proton in both rings, as shown in Fig. 1.

Nicotine exists in nature as a salt [2] and is processed to produce free-base nicotine [47]. Tobacco manufacturers have been accused of utilising alkaline substances (ammonia) to convert nicotine salt into its free-base form, allowing for efficient and rapid absorption [46]; it is believed that free-base nicotine can readily pass through the biological membrane in the respiratory tract, resulting in quicker absorption [46, 48]. In another study, DeVito et al. demonstrated that nicotine absorption is faster when it exists in the free-base form, with higher levels of alkalinity increasing the speed of absorption [13]. In addition, free-base nicotine is more volatile than

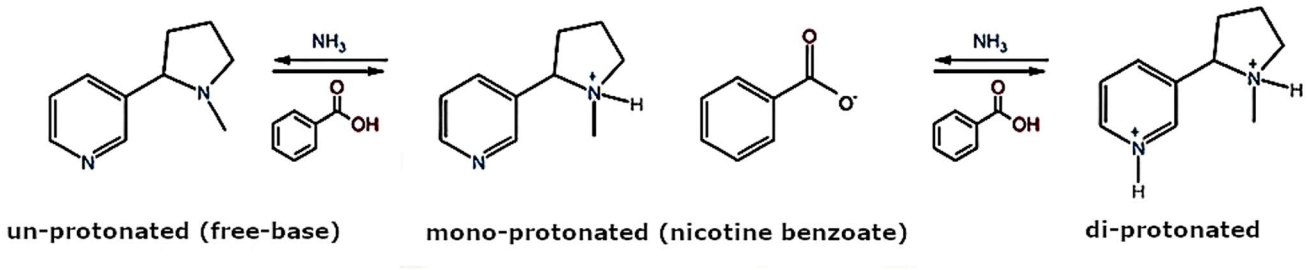


Fig. 1 Synthesis of nicotine salts and free-base nicotine (adapted from [2, 33, 46, 47])

nicotine salts and is more likely to reach receptors in the mouth and upper airway, resulting in stronger sensory reactions and, hence, a greater throat hit (nicotine harshness) [13, 44, 47]. According to other authors [13, 47], most e-liquids (including those without corresponding label specifications) contain free-base nicotine, which has been identified in up to 60% of e-liquids on the market. Scholars have observed that increases in the concentration of free-base nicotine lead to increases in the pH. However, the addition of acid counteracts the increases in pH, allowing the pH to remain low despite high nicotine concentrations, a condition present in nicotine salts. Therefore, understanding the composition of nicotine salts is crucial in distinguishing them from free-base nicotine.

2.2 Nicotine salts

As depicted in Fig. 1 [47], free-base nicotine is mixed with an acid, most commonly benzoic or citric acid [2, 47, 48], to prepare the nicotine salt. As indicated in Table 1, nicotine salts are considered more stable and less volatile than the free-base form, implying that the absorption of nicotine into the body increases in the presence of acids. However, they may not produce as much vapour as free-base nicotine e-liquids.

Nicotine salts have grown in popularity due to their ability to lower the pH, resulting in a smoother throat hit and allowing the vaper to inhale significantly high doses of nicotine [2, 47, 49, 50]. Some businesses produce nicotine salts at concentrations ranging from 56 to 75 mg/mL, fourfold higher than the amount permitted in numerous countries [51]. These amounts are considered high, particularly for young people who have never been exposed to smoking, whether in the form of conventional cigarettes or ECs. In several brands of nicotine salts, despite the high concentrations indicated on the labels, the measured values are oftentimes higher, as shown in Fig. 2. For example, the label "Nicotine River" lists a value of 48 mg/mL, while the measured value is 68.8 mg/mL [51]. In addition, the labelled value for "Crystal Canyon" is 24 mg/mL, while the measured value is 33.1 mg/mL [52].

Generally, the non-disclosure of nicotine levels in e-liquids or incompatibility with labelled values, even if minimal, is risky. This can lead inexperienced vapers to overdose, encouraging them to vape more due to the perceived safety in doing so [53]. For example, 37.4% of adolescent EC vapers have reported using nicotine-containing e-liquids, with 28.5% using nicotine-free ones; however, 34.1% were not aware of the nicotine concentration in the e-liquids they were using [13]. Cameron et al. have reported that 30–60 mg of nicotine in e-liquids is a deadly dose for adults, while 10 mg is a lethal dose for children if substantial amounts are consumed in a short period [54]. Notably, various salts can be found in a single e-liquid; a recent investigation by

Table 1 Comparison of nicotine salts and free-base nicotine (data taken from [2, 47, 48])

	Free-base nicotine	Nicotine salts
Protonation	Deprotonated by ammonia	Protonated via the addition of benzoic, citric, lactic, levulinic, or tartaric acid
In high doses	Harsh	Smooth
Strength	Suitable for low and medium nicotine strength in e-liquids	Suitable for high nicotine strength in e-liquids
Oxidation	Fast	Slow
Shelf life	Short	Long
Volatilisation	More volatile than nicotine salts	Less volatile than free-base nicotine

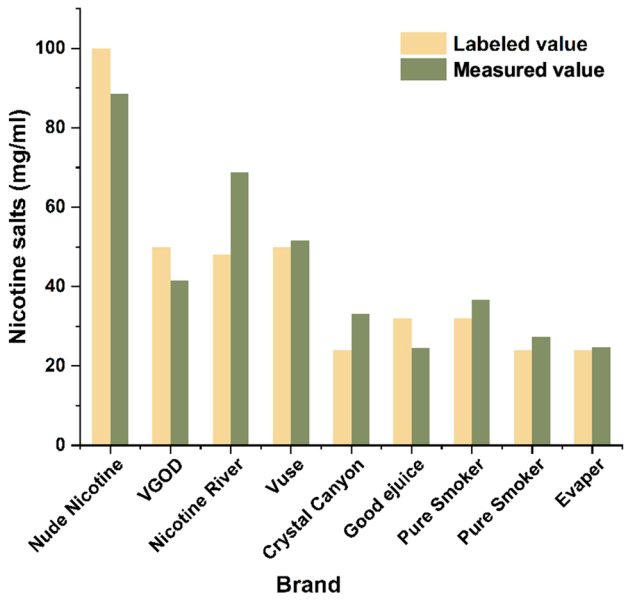


Fig. 2 Labelled and measured concentration values for several brands of nicotine salt (data taken from [40, 47, 48, 51, 52])

Harvanko et al. revealed that of 23 e-liquids that contained nicotine salts, while most comprised only one salt, three contained multiple acids [47]. In summary, this section has provided critical insights into the effects of nicotine salts and free-base nicotine and how to convert from one form to the other. However, further research is needed to elucidate the conversion of nicotine to alkaloids by examining the stability of nicotine within e-liquids.

3 Nicotine stability

Understanding the stability of nicotine in e-liquids is essential for its accurate quantification and studying its long-term decomposition. This section discusses the fundamental issues of nicotine stability during storage and its sensitivity to flavours and power/temperature changes.

3.1 Storage conditions

Nicotine is the primary alkaloid in e-liquids; as explained earlier, its extraction from tobacco may lead to the formation of certain contaminants, known as secondary alkaloids [5, 55, 56], high levels of which may suggest poor handling or storage [34]. Secondary alkaloids arise from the oxidation of flavour compounds in unstable formulations and exposure to high temperatures [57]. Many studies have demonstrated that unstable formulations or interactions with packaging materials are problematic and increase nicotine degradation [43, 58]. The US Food and Drug Administration (FDA) has identified the presence of secondary alkaloids in most analysed samples, but these compounds are present at much lower levels than nicotine [38, 44, 59]. Nonetheless, e-liquids must be kept in firmly closed opaque containers to avoid exposure to air or light, factors that can convert nicotine into secondary alkaloid compounds [57, 60, 61]. More recent research efforts have focused on nicotine decomposition in e-liquids and its transformation into secondary alkaloids over time; however, no mainstream products have been identified as having a secondary alkaloid concentration above 2% [31, 62]. Thus, other factors, such as the presence of chemicals used as flavouring agents, must be considered as these may have an impact on the product in terms of altering the characteristics of the e-liquid.

3.2 Sensitivity to flavours

While few studies have investigated the sensitivity of nicotine to flavours, these have had a significant influence on the development of new concepts regarding flavours. Chemicals are added individually or as a mixture to generate a non-tobacco-like aroma or flavour [63]. Many flavours, including fruit, mint, and vanilla, can lead to the disintegration of nicotine via oxidation reactions [34], rendering e-liquids unusable in a short period of time [57]. Flavours differ in strength (ultra-light, light, mild, or full-flavoured) and often undergo multiple chemical and physical transformations when heated, although certain low-volatility flavouring additives, such as herbs and caramel, exist [3, 64]. Most manufacturers do not describe the flavours in their entirety and instead employ generic terms such as “truth serum”, “snake oil”, and “rhino blood” [57]. Some secondary alkaloids are no longer detectable after 2 months, whereas the flavours of others, such as N-oxide, increase sharply due to increases in temperature and humidity during storage. It is therefore critical to evaluate the compatibility of flavours with nicotine and conduct stability testing to ensure that the target nicotine levels are maintained throughout the shelf life of the e-liquid.

Some developers have added unconventional flavours to e-liquids and filed patents in this regard [65], with recent findings suggesting the high popularity of strong flavours, potentially contributing to the formation of new habits [66]. Some vapers opt for devices with manual power control to ensure the optimal experience [67]. Thus, beyond long-term storage and the addition of strong flavours, external factors, such as the device settings and changes in power or temperature, are important to consider.

3.3 Sensitivity to changes in power or temperature

ECs generate aerosols by delivering energy to an atomiser, which raises the temperature to transform the e-liquid into

an aerosol [13, 68, 69]. Compared to the early generation models, which had nonadjustable power settings, modern/new-generation EC devices are more advanced and allow for manual adjustment of the power settings [3, 10, 70]. Scholars have hypothesised that increasing the power increases the quantity of volatile nicotine and, hence, leads to higher nicotine levels in the generated aerosol [71]. Notably, delivering nicotine in large quantities increases the health risks associated with the use of ECs [32, 72, 73]. García-Gómez et al. experimented with three e-liquids, highlighting the impact of power changes on the aerosol composition [74]; the maximum power setting (35 W) resulted in a 40-fold increase in the nicotine content in the aerosol compared to the minimum power (5 W). However, Peace et al. noted that the increase is not linear, making it impossible to predict the quantity of nicotine that is transferred to the aerosol using a specific power [1]. In another study, El-Hellani et al. reported that the power was changeable in the range of 2.18–6.96% and detected an associated decrease in the nicotine content with increased power [75]. Nonetheless, the experimental data are rather controversial, and there is no consensus on the relationship between the quantity of nicotine in EC aerosols and the power setting; this highlights the need for the standardisation of ECs to enable nicotine quantification.

4 Optimum instrumentation for nicotine quantification

Considering that the components of ECs are separated into the vapour and liquid phases, this section compares the limits of detection (LODs) of nicotine between the two phases to determine the most suitable analytical conditions. The aim is to meet quality assurance (QA) standards, which involve implementing systematic processes to determine whether a product meets the requirements for sale to the public.

4.1 Liquid phase

Nicotine is a soluble compound and one of the most common components that can be analysed via chromatographic methods, such as gas chromatography (GC), liquid chromatography (LC), and high-performance liquid chromatography (HPLC). As indicated by Geiss et al., the LOD of nicotine measured via GC-flame ionisation detection (GC-FID) is 1 µg/mL, where repeated dilutions (up to approximately 667 fold) were performed prior to injection for enhanced direct injection (DI) during the nicotine analysis [76]. Meanwhile, Goniewicz et al. used GC with a thermionic specific detector (GC-TSD) and observed an LOD of 50 ng/µL [77]. In addition, dissolving the sample in methanol with vigorous shaking for 10 min yielded a high nicotine content [78]. Elsewhere, Trehy et al. analysed e-liquids using HPLC with a diode array detector (HPLC–DAD) to compare the gradient and isocratic elution methods; the LOD of nicotine was determined as 0.1 ng/µL, with its isocratic value ranging between 0.3 and 34 ng/µL, indicating lower sensitivity [30]. While HPLC with photodiode array (HPLC–PDA) detection is widely employed in analyses, its sensitivity is not as high as that of mass spectrometry. Furthermore, while it offers spectral information, it fails to provide detailed structural information; thus, additional techniques, such as mass spectrometry, may become necessary.

4.2 Vapour phase

To collect vapour particles, an appropriate tool, such as an adsorbent cartridge, bag sampler, or sorbent tube, is necessary. The simplest and least complex approach entails using sorbent tubes (e.g., XAD-4, Tenax-TA/TD, and Anasorb CSC) lined with solid materials (adsorbent compounds), where the collected samples can be analysed via two methods: extraction with a solvent, or using a thermal desorber (TD), which is the most common approach. Sorbent tubes function as a sample collection medium in both the liquid and vapour phases and present several advantages, including high sensitivity, rapid analysis, and the ability to collect samples without coming into contact with them. Nicotine in the aerosol phase has also been analysed using GC coupled with a nitrogen phosphorous detector (GC-NPD) together with the XAD-4 solvent extraction method, yielding an LOD of 0.22 µg/mL [79]. Similar studies using GC-mass spectrometry (GC–MS) with a sorbent tube (Tenax-TA/TD) for nicotine analysis have achieved an LOD of 0.6 µg/mL. Among these methods, GC–MS is noted for its sensitivity and selectivity in nicotine analysis. While it is effective in analysing nicotine in EC aerosols, analysis in the liquid phase requires the derivatisation of nicotine with, for example, a trimethylsilyl (TMS) group or *N*,*O*-bis(trimethylsilyl)trifluoroacetamide (BSTFA) to increase its volatility [76]. Overall, the compounds found in e-liquids [such as propylene glycol (PG), glycerol or vegetable glycerin (VG), and nicotine] can be accurately identified and quantified using GC with FID or MS.

Many pollutants can be released in both the liquid and vapour phases, though in differing quantities depending on the phase. Nicotine is detectable in both phases; consequently, it is preferable to compare the labelled and measured values to determine the separation efficiency and validate the labelled concentrations.

5 Differences between labelled and measured concentrations

The accurate labelling of e-liquids is important to ensure that vapers do not use incorrect doses or overdose, situations that can prove toxic. This section highlights the analytical

measurements of various nicotine and nicotine-free e-liquids in comparison to the labelled values of these products.

5.1 E-liquids with varying nicotine concentrations

According to the product labels, the nicotine content in e-liquids ranges from 0–36 mg/mL [3, 9], in some cases surpassing the limit of 20 mg/mL recommended by guidelines [37]. Furthermore, some e-liquids have been found to contain 88.6 mg/mL of nicotine [47]. Assessing the safety of ECs and e-liquids is problematic because of the variety of e-liquids and devices available, meaning that it is possible to find different quantities of nicotine in e-liquids classified as containing the same concentration [80]. According to multiple investigations, discrepancies exist between measured nicotine levels and those provided on product labels, as shown in Table 2. A detailed examination of 32 e-liquids by Bennani et al. showed that 31% of the analysed products accurately indicated the quantity of nicotine. Nonetheless, 47% revealed a mismatch of more than 20% between the measured and labelled values [43]. Similarly, another study found that the nicotine concentration of 18 of 27 e-liquids deviated by more than 10% from that listed on the labels, with the discrepancy in the remaining nine exceeding 20% [25], raising questions about the reliability of the labels. In another investigation, 19 samples exhibited higher nicotine levels, in the range of 0.3–77%, and 13 displayed lower levels, ranging from 0.2 to 96.3%, compared to the labelled values [81]. In contrast, some reports have revealed that the measured values correspond to (or are lower than) the labelled values [52, 82, 83]. In 2020, Jackson et al. reported a decrease in nicotine concentrations in 23 of 24 e-liquids using LC-tandem mass spectrometry (LC–MS/MS) [84]. This suggests that the disparity between the labelled and measured nicotine values is smaller than previously reported, revealing improvements in the production process over time [17, 34]. Comparing labelled and measured concentrations in nicotine-free e-liquids may also constitute a noteworthy area of future research.

5.2 *Nicotine-free e-liquids*

The terms "nicotine-free", "without nicotine", "no nicotine", and "zero nicotine" refer to e-liquids without nicotine, suggesting that they are safer than nicotine-containing ones and NCs [30, 32, 88, 89]. Alhusban and Ata tested 11 e-liquids, including one labelled as "nicotine-free", in which no nicotine was detected [26]. Bansal et al. tested 12 e-liquids, including one labelled as "nicotine-free"; again, the findings indicated the absence of nicotine [85]. Finally, in the study by Chivers et al., four of ten nicotine-free e-liquids did not contain nicotine, while the remaining did [90].

While some e-liquids have been labelled as being free of nicotine, their analysis has revealed the presence of nicotine [17, 30]. Notably, Saffari et al. executed a study on the labelled and measured values of nicotine resuspension,

Table 2 Summary of literature findings on measured and labelled nicotine levels in e-liquids

No. of samples	Units	Nicotine strength	[a]Division from label (%)	Phase selection for analysis		Detector	References
				Liquid phase	Vapour phase		
HPLC						PDA	[26]
11	mg/mL	0–25	− 63.1 to + 3.24	●			
12	mg/mL	0–18	+ 12 to + 17.9	●		PDA	[85]
12	mg/mL	3–6	− 37.34 to + 12.34	●		MS/MS	[84]
27	mg/mL	6–22	− 55 to + 39	●		PDA	[25]
30	µg/100puffs	0–43.2	NA		●	PDA	[30]
32	mg/mL	3–24	− 100 to + 3.3	●		PDA	[43]
GC						TSD	[86]
32	mg/mL	0–18	− 32.2 to + 3.3	●			
36	mg	0–24	− 38 to + 3.8	●		MS/MS	[60]
21	mg/mL	12–18	− 21 to + 22.2	●		FID	[87]
72	mg/mL	0–12	− 96 to + 83	●		MS	[81]
72	mg/13puffs	0–12	NA		●	MS	[81]
NA	mg/150puffs	0–24	NA		●	TSD	[77]

Nicotine strength = labelled value of the nicotine provided by the manufacturer

mg/mL milligrams per millilitre, *µg/100 puffs* micrograms per 100 puffs, *mg* milligram, *NA* not available, *HPLC* high-performance liquid chromatography, *GC* gas chromatography, *PDA* photodiode array, *MS/MS* tandem mass spectrometry, *TSD* thermionic specific detector, *FID* flame ionisation detection, *MS* mass spectrometry

[a]Division from label (%) $= \frac{\text{measuredvalue} - \text{labelledvalue}}{\text{labelledvalue}} \times 100\%$

observing small differences between them; these differences were related to the resuspension of nicotine with particles in the chamber throughout the sampling [91].

Beliefs about the absence of nicotine can impact EC use behaviour. To explore this, two self-administration sessions were conducted with a group of vapers, who were given two nicotine-free e-liquid options. However, in one session, they were told that the products contained nicotine; unexpectedly, the participants reported fewer vaping cravings and lower vaping intentions following this session compared to the "no nicotine" session [25]. Numerous studies have revealed the presence of nicotine in measurable levels in nicotine-free e-liquids, raising concerns about the lack of quality control standards [2, 90, 92]. As illustrated in Fig. 3, the nicotine concentration in sample (A-3) reaches 21.80 mg/cartridge of nicotine in one e-liquid registered as nicotine-free [30], with the remaining samples displaying even more disparity. Sample (B-2) contains 23.91 mg/mL nicotine, a notably high concentration for an e-liquid classified as nicotine-free [92].

Notably, some brands do not use units to express the nicotine level and employ ambiguous expressions, leading to uncertainties. For example, some brands include "30 mg" or "30" on the label, which could refer to a content of 30 mg nicotine in the cartridge or a concentration of 30 mg/mL [93]. Other brands do not list the nicotine concentration as a number and instead use qualitative terminology ("low", "medium", or "high"); such terms complicate the interpretation of the nicotine content as they cover a wide range of nicotine concentrations [54]. While medicines and drug delivery devices are subjected to manufacturing standards, ECs are not [34, 94], and their manufacturers do not provide detailed information about their composition in the manufacturing or synthetic process [94]. As a corollary, e-liquids are not completely label-compliant and may include contaminants and other compounds generated or released by vapers during aerosol formation.

6 Other compounds found in e-liquids

E-liquids contain several other common and less common components, including water, PG, and VG [5, 95–97]. Furthermore, the flavouring compounds can include carcinogenic substances [5, 98]. These components interact with parts of the EC device, leading to the unintentional generation of both volatile organic compounds (VOCs) and non-VOCs due to, for example, high temperatures and oxidation processes [99, 100]. This section focuses on these e-liquid components (both VOCs and non-VOCs), whether they are produced directly or indirectly, and the reasons for their generation.

6.1 Common compounds

6.1.1 Volatile organic compounds (VOCs)

The most common organic compounds volatilise under ambient temperature and pressure conditions [91]. Various studies have confirmed the existence of VOCs in e-liquids. For example, formaldehyde—a colourless and combustible compound that causes irritation to the eyes, nose, and throat—has been categorised as a VOC with a low molecular weight [5, 101–103]. Acetaldehyde is also present as a flavour compound in some e-liquids [5], though it is recognised as less hazardous than formaldehyde [category 2B, according to the International Agency for Research on

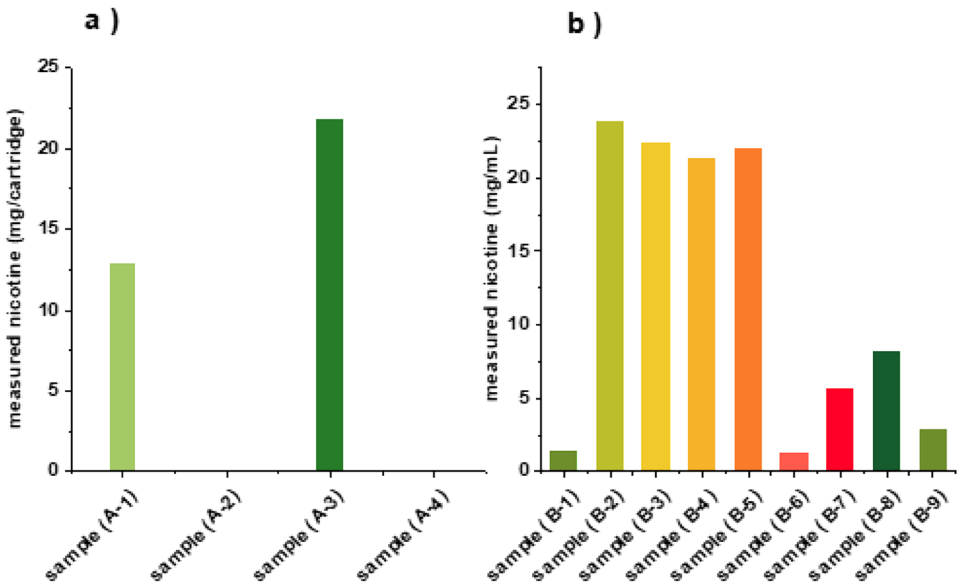
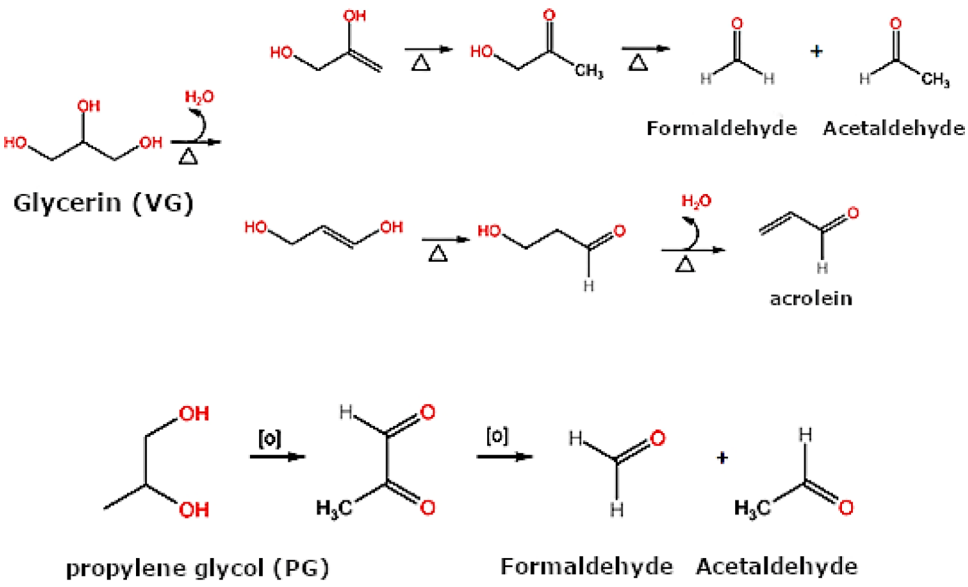


Fig. 3 Average nicotine levels measured for e-liquids labelled as "nicotine-free", showing **a** the total nicotine in the cartridge and **b** the proportion of nicotine (mg/mL; data taken from [17, 26, 30, 90, 92, 93])



Scheme 1 Pathways for the dissociation of vegetable glycine and the oxidation of propylene glycol (taken from [104–107])

Cancer (IARC)]. Acrolein is another common compound found in e-liquids; it exists as a colourless or pale yellow water-soluble liquid with a strong odour and evaporates when heated. Furthermore, it is corrosive and can cause damage to the lining of the lungs as well as nasal cavity irritation [5]. Meanwhile, benzene (category 1, according to the IARC), an aromatic hydrocarbon, can lead to health concerns, including the risk of cancer, when inhaled. Some VOCs (toluene, styrene, and xylene) have been found in e-liquids after being used as solvents for extracting nicotine from tobacco leaves [34]. Changing the conditions of e-liquids can result in the formation of new compounds or increase the concentration of existing ones. Humectants, such as PG and VG, prevent the fluid in ECs from drying and ensure the formation of an aerosol upon heating the e-liquid by the atomiser [5, 26, 103]. Either PG or VG or both can be present in e-liquids, though PG is the most common (over 90%) [5, 102]. PG is produced via the hydrogenation of propylene oxide at high pressures and temperatures, whereas VG is generated from plant oils [5, 69]. While these two compounds are considered safe by the US FDA, in ECs, they are heated to form aerosols and can produce hazardous carbonyl compounds [5]. According to previous investigations, acrolein, formaldehyde, and acetaldehyde can be produced in EC aerosols via the heating of PG/VG, as depicted in Scheme 1 [104–107]. The concentration of carbonyl compounds can also increase when they encounter the nichrome wire in the atomiser, possibly enhanced by the heating [101]. Because EC manufacturers do not offer comprehensive information about the substances employed during the manufacturing process, several studies have recommended the systematic quality control of e-liquids and ECs [5, 6, 9, 91].

6.1.2 Analysis of carbonyls in e-liquids

Laugesen used selected ion flow tube mass spectrometry (SIFT-MS) to identify acrolein and acetaldehyde in e-liquids, observing an LOD of 0.3 ng/µL [102], and in another study, Lim and Shin measured the LODs of formaldehyde (13.1 ng/mL), acrolein (3.5 ng/mL), and acetaldehyde (6.3 ng/mL) [108]. The chemical composition of the aerosol may differ from that of the e-liquid due to temperature variations, resulting in chemical reactions that yield new compounds. Consequently, numerous researchers have found that low-molecular-weight compounds, including formaldehyde, acetaldehyde, and acrolein, are generated in large quantities upon heating e-liquids [109, 110].

6.1.3 Analysis of carbonyls in the EC vapour

PG oxidation yields formaldehyde and acetaldehyde during the heating of e-liquids, and the fragmentation of VG at high temperatures results in the generation of carbonyl compounds [5, 101]; these processes can be attributed to their low molecular weight [5]. Goniewicz et al. used HPLC with DNPH to quantify several compounds in aerosols, including formaldehyde, acetaldehyde, and acrolein [77, 111], observing variations between 0.01 and 0.1 µg/mL in the LODs. Elsewhere, Schripp et al. detected formaldehyde and acetaldehyde using GC–MS, reporting LOD values in the range of 0.0016–0.002 µg/mL [107]. In addition, GC–MS has been utilised to identify acrolein and acrylamide, yielding LOD values ranging from 8 to 270 ng/mL [112]. The compounds in ECs can be categorised as direct compounds, already present in the synthesised e-liquid, and indirect compounds, newly generated from oxidation processes or temperature

changes. In the case that indirect compounds are present in the e-liquid, heating increases their concentration. Phase selection is critical to achieving optimal outcomes, with the vapour phase including more volatile and carbonyl compounds than the liquid phase. While researchers tend to focus their efforts on analysing compounds commonly found in e-liquids, one should also note the possible presence of other less common compounds.

6.2 Uncommon compounds

Mixtures of phenolic derivatives are generated from industrial processes [113, 114] during the production of pesticides or pharmaceuticals. Phenols are major pollutants in wastewater; most are toxic and classified as hazardous compounds that produce an unpleasant taste and odour upon reacting with chlorine to form chlorophenols [113]. In this context, these compounds have become a cause for concern due to the associated health risks [114]. Chlorinated organic compounds and chlorophenols are considered priority water pollutants, presenting a danger to aquatic organisms [115, 116], and are derived from petroleum minerals, plastics, rubber, and pharmaceuticals [117, 118]. According to the literature, the presence of pollutants such as 2-chlorophenol has been identified in sewage water and other waste products. In 2019, scholars tested e-liquids (nicotine-free) to detect both nicotine and organic compounds [90], with 2-chlorophenol being observed in all 10 samples. One should also note that the detection of components such as 2-amino-octanoic acid, a metabolite found in mammalian blood, faeces, and urine, indicates the presence of biological pollutants during manufacturing. Here, it is critical to note that ECs are not manufactured in accordance with the regulatory requirements imposed on products such as drug delivery devices. Furthermore, refilled e-liquids and cartridges may not adhere to the labelled contents, increasing the possibility of the presence of impurities or toxic substances [119, 120]. Further investigations and experiments on the role of ECs in smoking cessation are, thus, highly recommended.

7 Do electronic cigarettes help one to quit smoking?

The major risk associated with e-liquids involves the wide range of nicotine doses available. Notably, some e-liquids can comprise nicotine levels of 75–100 mg/mL [47], severalfold higher than the allowed level. Earlier research studies have also revealed that nicotine delivery by ECs equals or exceeds the levels in NCs [7, 121]. In addition, the same investigations that evaluated the biomarkers of nicotine exposure in vapers and smokers identified similar nicotine levels in these groups [122, 123]. Despite their increasing popularity, however, ECs still represent a novel vaping technique. To the best of our knowledge, no long-term in-depth studies have been conducted to explore associated clinical abnormalities; nevertheless, even short-term exposure (approximately 15 min) has harmful consequences at both the organ and cellular levels [3, 124, 125]. Furthermore, ECs are not risk-free products and cannot be declared safe for use until an authoritative judgement is made regarding their clinical effects [126]. Each year, 52% of smokers attempt to quit, though relapse rates remain high: most vapers fail to quit, and only 6% manage to do so [127].

Many public health organisations have expressed concerns about the health effects of ECs [82, 128]. In 2012, the European Respiratory Association stated that, according to prevailing information, ECs are not a safe alternative to smoking. In the same year, the International Air Transport Association (IATA) recommended that ECs be banned on all aircraft [9]. Furthermore, in 2016, the US FDA introduced packaging, refilling, and labelling requirements to ensure accuracy in the recording of nicotine contents [85]. However, the FDA has not established specific acceptable emission guidelines [98]. Nonetheless, neither the US FDA nor the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) promote the use or distribution of ECs, and the World Health Organisation (WHO) has indicated that a lack of evidence precludes ECs from being considered a viable method for quitting smoking [9].

8 Conclusion

This literature review discussed the variations in the types of nicotine used in ECs. Since nicotine salts have a lower pH (due to the addition of acids), the throat hit is less harsh and smoother; they are, thus, available in higher quantities. On the other hand, free-base nicotine has a higher pH and is, hence, more alkaline, resulting in a less smooth and harsher throat hit; it is also more readily available in low to medium dosages. Nicotine stability in e-liquids is crucial for ensuring product quality. For instance, nicotine is oxidised and converted into secondary alkaloids upon exposure to air or light; thus, to preserve its stability during storage, e-liquids need to be firmly sealed and kept in a cold, dark room. Furthermore, some flavours interact with nicotine, leading to its degradation into secondary alkaloid compounds and a decrease in its concentration. The process of vaporising e-liquids and delivering nicotine is influenced by temperature: nicotine evaporation is reduced at lower temperatures and increases at higher temperatures. In the latter case, higher temperatures increase the possibility of generating compounds not initially present in the e-liquid, such as formaldehyde and acrolein, or enhance the presence of compounds such as acetaldehyde, which is used as a flavour compound in

some ECs. Since the long-term effects of e-liquid use are yet unknown, further and more thorough research is recommended to validate the safety and quality of e-liquids and analyse their potential consequences. Future research efforts can also examine the possible outcomes of using high-nicotine e-liquids—containing, for example, nicotine salts or alkaloid compounds—by conducting longitudinal data analyses on the health outcomes of diverse populations.

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Declarations

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