

# E-Cigarette Toxicology and Public Health — Exploring the Safety of E-Cigarette Compared to Traditional Cigarette

Xiyu Wang\*

Department of Biology, University of Toronto at Mississauga, Mississauga, Ontario, Canada

\*Corresponding author: Xiyu.wang@mail.utoronto.ca

**Abstract.** With the popularity of e-cigarettes, there are concerns about the potential health risks associated with inhaling e-cigarette aerosols, which contain a complex mixture of chemicals including nicotine, flavourings and poisons. This paper presents a systematic toxicological analysis of several chemicals commonly found in e-cigarettes. The chemical properties and toxicity of nicotine, propylene glycol, vegetable glycerin, benzaldehyde and cinnamaldehyde are discussed in relation to their use in e-cigarettes, with an emphasis on the hidden health risks involved. Nicotine is a highly addictive alkaloid that causes oxidative stress, neuronal apoptosis, DNA damage, and is highly toxic. E-cigarette solvents, such as vegetable glycerine and propylene glycol, can activate melanin production in the skin and raise the likelihood respiratory infections. Flavouring agents like benzaldehyde and cinnamaldehyde can induce cellular damage and heighten the susceptibility to disease like cancer and cardiovascular disease, particularly in individuals with specific genetic variants of the ALDH2 enzyme. The discussion revealed a lack of research to fully understand and assess prolonged health effects of e-cigarette use. However, both clinical and marketing should highlight the known possible risks. Clinicians should advise patients accordingly, and regulators must closely monitor the sale and promotion of e-cigarettes and be transparent about any potential harms to safeguard the welfare of consumers.

**Keywords:** E-cigarette; Nicotine; Vegetable glycerin; Propylene Glycol; Benzaldehyde; Cinnamaldehyde; Toxicology; Public health.

## 1. Introduction

Throughout history, humans have consumed tobacco for various purposes, including religious and medicinal uses, and as a stress-reliever and social activity [1,2]. However, as the primary substance used in the act of smoking, tobacco is now considered one of the major contributors to the human health burden and becomes the main public health issue. According to the World Health Organisation, 22.3% of people worldwide are tobacco users, with men being the majority [3]. Tobacco kills over 8 million people each year, of which 7 million direct users and the remainder as second-hand smoke victims [3]. As the most common substance of abuse today, tobacco use is considered as one of the risks of causing degenerative diseases such as cardiopulmonary vascular disease and cancers [4]. With over 2550 compounds known to be present in tobacco and more than 4000 compounds in the smoke, it poses a significant biohazard, with over 43 carcinogenic compounds, including nicotine, tobacco-specific nitrosamines, and alpha-emitting radionuclides being the primary hazards [1]. Tobacco smoke also contains substances such as carbon monoxide, thiocyanates and tar, which can negatively affect almost every living cell in the body [1]. Consequently, all forms of tobacco use are deemed detrimental, with no safe level of exposure.

Cigarette smoking remains the most prevalent way of tobacco intake worldwide, although there are numerous ways of consumption [3]. As more people become aware of the harmful effects of tobacco, society is pushing for people to avoid smoking altogether, and for smokers to quit. However, cessation is not an easy process, which is why less harmful tobacco and nicotine products are being recommended as an alternative to cigarettes to reduce the harm to smokers. One such product is the electronic cigarette or electronic nicotine delivery system, which is introduced as a safer alternative to traditional cigarettes and has sparked controversy worldwide [5]. These electronic products typically composed of a cartridge that comprise e-liquid, a heating element, and a rechargeable battery. And the smoking-like experience is provided by atomising the e-liquid containing moisturizers,

flavourings, and sometimes nicotine [5]. As nicotine is a key factor in tobacco addiction, e-cigarettes without or with varying concentrations of nicotine are often used as smoking cessation tools [5]. Their easy accessibility, smokelessness, portability, and versatility in flavour and appearance have also made them a sensation among young people [5]. In just a few years, there has been a huge spike in the incidence of e-cigarette consumption in teens, surpassing those observed in adults [6,7]. Common reasons for young adults using e-cigarettes include curiosity, influence from friends or family, and the perceived health benefits [7].

While most manufacturers claim that e-cigarettes do not cause any harm and can even benefit health, the heating process has been reported to lead to the production of potentially harmful breakdown compounds [5]. E-liquids used for combustion typically consist of nicotine, propylene glycol, glycerol, flavourings, and water [7]. Although, scientific evaluations of e-cigarettes now indicate that the exact level of risk they pose is yet to be definitively determined, they are not entirely risk-free [8]. Inhalation of e-cigarette aerosols is considered harmful to various body systems, including the lungs, mouth, and gastrointestinal tract [8]. The diverse flavours, e-liquids, and device materials all contribute to the possible toxicity, which makes the chemistry of e-cigarette aerosols more complex than that of e-liquid alone [8]. Harmful chemicals related to flavour, such as diacetyl, cinnamaldehyde, and benzaldehyde, also differentiate the aerosol from electronic cigarettes from the smoke of traditional cigarettes [8]. These compounds are often difficult to identify and have low molecular weights and boiling points, such as metals, permanent gases, aromatic species, and nitro compounds [8].

E-cigarettes are frequently advertised as harmless, but their safety is often questioned. To address these concerns, a systematic toxicological analysis of e-cigarettes is required. This paper aims to conduct such an analysis, focusing on the most commonly found chemicals in e-cigarettes: nicotine, vegetable glycerine and propylene glycol, and benzaldehyde and cinnamaldehyde. The toxicity and safety of these compounds will be comprehensively discussed.

## 2. Nicotine

Nicotine ( $C_{10}H_{14}N_2$ ) is a highly addictive plant alkaloid consisting of pyridine and pyrrolidine rings [9]. In its pure state, nicotine is a clear liquid with an oily consistency; while it turns into a brown liquid and gives off a strong tobacco smell when exposed to air [10]. As a weak base, nicotine does not possess the ability to cross membranes rapidly after ionisation [9]. However, after inhalation, nicotine reaches the small airways and alveoli and is rapidly absorbed due to the increase of ambient pH [9]. In other words, the pH of the solution determines the absorption and availability of nicotine [10]. Common absorption points in the human body are the oral mucosa, lungs, and skin [10]. After absorption, nicotine can affect the central nervous system by binding to nicotinic acetylcholine receptors and mediating neurotransmitters releasing [9]. As an agonist of the nicotinic acetylcholine receptor, nicotine can stimulate ganglia at low doses and block ganglia at high doses [9]. Common neurotransmitters that can be modulated by nicotine intake are acetylcholine, dopamine, norepinephrine, serotonin, endorphin [11]. Nicotine can also trigger the chemoreceptor trigger zone in medulla oblongata, the vomiting centre in brain [11]. Once ingested, nicotine is absorbed and metabolized by the liver via two phases. In the first phase, nicotine is oxidised by microsomes to form various metabolites, such as cotinine and nonidine [10]. In the second phase, the metabolites produced have N'- and O'-glucuronidation and are excreted in the urine, faeces and bile [10]. A small proportion of unaltered nicotine can be excreted via the kidneys [10]. Nitrosation of nicotine in the body produces the highly carcinogenic N-nitrosocotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone [10].

The use of nicotine results in acute effects on both the prefrontal cortex and the visual system, which manifest as increased activity in these regions [10]. Furthermore, nicotine has a positive impact on pharmacological reward by regulating the release of various neurotransmitters [10]. Despite these, nicotine can enhance oxidative stress, neuronal apoptosis, and DNA damage [10]. By acting on nicotinic acetylcholine receptors, nicotine can promote angiogenesis accompanying by  $\beta$ -adrenergic

activation [10]. Nicotine can enhance proliferation and survival in cancer cell by binding to Bcl2 and COX2 or activate NF- $\kappa$ B [10]. Nicotine also inhibits apoptosis by phosphorylating the extracellular signal-regulated kinases of Bcl2 [10]. Direct application of nicotine on exposed areas can cause a burning sensation, increased salivation, and symptoms such as nausea, tachycardia, and elevated blood pressure [10]. Nicotine can also increase plasma free fatty acids and blood glucose levels, as well as the levels of catecholamines in the blood, resulting in increased blood viscosity [10]. Nicotine is a highly toxic poison that affects both the peripheral and central nervous system [10]. In cases of severe poisoning, tremors, paralysis, cyanosis, collapse and coma can occur [10]. Death may even occur from respiratory muscle paralysis and central respiratory failure [10]. The LD50 for adults is approximately 30-60 mg of nicotine. The LD50 for children is approximately 10 mg [10].

### 3. Vegetable Glycerine and Propylene Glycol

Vegetable glycerine ( $C_3H_8O_3$ ) and propylene glycol ( $C_3H_8O_2$ ) are the fundamental ingredients in e-cigarette solvents to dissolve flavourings and nicotine and provide a throat hit similar to that of a cigarette. Vegetable glycerine is a clear, viscous non-polar liquid with a sweet odour [12]. It is soluble in water and most non-polar solvent, but not in hydrocarbons [12]. It is also known as the “mini-sugar” because it has three hydroxyl groups that form strong hydrogen bonds intermolecularly [12]. Because of its weak acidity, it can also readily interact with basic hydroxyl groups [12]. Propylene glycol is a synthetic organic compound with two hydroxyl groups and has an extremely high water absorption capacity [12]. It is a colourless, viscous liquid with bitter flavour [12]. The chemical properties of vegetable glycerine and propylene glycol make them promising for a wide range of industrial and academic applications. Vegetable glycerine and propylene glycol are the first chemicals that interact with the epithelial cells of the mouth when the e-cigarette is heated [13]. The faux-smoking impact of e-cigarettes in the throat is largely attributed to propylene glycol, whereas the large aerosol clouds generated by heating e-cigarette originate from vegetable glycerine [13]. Although propylene glycol is less palatable than vegetable glycerine, e-liquids containing propylene glycol systematically deliver more nicotine, almost doubling the yield, compared to those containing vegetable glycerine [13]. However, 80% to 90% of e-cigarette solvents on the market are a mixture of vegetable glycerine and propylene glycol.

E-cigarette liquids containing propylene glycol can activate melanin production in the skin in a concentration-dependent manner, whereas vegetable glycerine alone does not activate melanin production [13]. Although, high doses of vegetable glycerine and propylene glycol result in high cytotoxicity, the proportion of these two chemicals in e-cigarettes is still crucial, as different ratios produce different effects [13]. Oral pigmentation can cause aesthetic problems, hinder the success of gingival decolourisation treatments, as well as be associated with oral mucosal melanoma [13]. Propylene glycol is considered as the main factor driving cytotoxicity, while vegetable glycerine has smaller effects [13]. The discrepancy in cytotoxicity can be attributed to two reasons: first, propylene glycol is less permeable due to being more hydrophobic, as it has one less hydroxy group than vegetable glycerine; second, propylene glycol has a structure similar to ortho-diphenols that increases the likelihood of forming quinone-like structures [13]. A combination of propylene glycol and vegetable glycerine is known to stimulate TRPA1 and TRPV1, which are co-expressed by melanocytes with  $Ca^{2+}$  permeable cation channels [13]. Propylene glycol is thought to be associated with the production of free radicals and to induce oxidative stress, while vegetable glycerine is linked with increase of aerosol particles and the attachment of bacteria to teeth [13]. The degradation of vegetable glycerol and propylene glycol results in dihydroxyacetone, a well-known skin tanning agent [13]. Furthermore, the aerosol produced by heating the e-cigarette solvent contains a small oligomer that could contribute to cytotoxicity [13].

## 4. Benzaldehyde and Cinnamaldehyde

Benzaldehyde ( $C_6H_5CHO$ ) consists of a benzene ring with a formyl group. It is a clear or yellowish liquid with a characteristic bitter almond smell [14]. As a common flavouring agent in food, benzaldehyde is one of the main ingredients in natural fruit flavours and is often used in cherry flavours [15]. Pure benzaldehyde is denser than water and insoluble in water when in liquid state and is heavier than air in gaseous state [14]. Benzaldehyde can undergo different reactions like oxidation and reduction, giving various products. It is not known to accumulate in any human organ and forms a conjugate with glycine or glucuronic acid and is excreted in the urine [14].

Cinnamaldehyde ( $C_9H_8O_2$ ) is a natural compound found in spices like cinnamon, with strong antiviral, antiseptic, and antibacterial abilities [16]. It consists of a benzene ring, an aldehyde group, and an unsaturated double bond, which gives cinnamaldehyde high oxidative properties at room temperature with or without catalysts [16]. However, oxidation can cause cinnamaldehyde to lose sterilization and anti-corrosion functions, which restricts its application as a food additive [16]. Common oxidants used in cinnamaldehyde oxidation studies are  $O_2$ ,  $NaClO$ ,  $H_2O_2$  and common catalysts are N-heterocyclic carbene, porphyrin,  $\beta$ -cyclodextrin, and iridium trichloride-cerium sulphate [16]. These catalysts and oxidants are reagents commonly used in the preparation and storage of cinnamaldehyde. Oxidation occurred without catalyst is due to the unstable conjugated bonds and aldehyde group [16].

Aldehydes used in e-cigarette as flavourings are a main concern of the safety upon usage. Aldehydes are highly reactive and can cause harm to cells, and even cause mutations or cancer [17]. To mitigate the harmful effects of these aldehydes, the enzyme ALDH2 in human body converts reactive aldehyde to a less harmful form [17]. However, humans with a specific genetic variant of ALDH2, called ALDH2\*2, have a reduced ability to metabolize these aldehydes [17]. This, combined with frequent exposure to environmental aldehydes, may enhance susceptibility to disease such as cancer or cardiovascular disease [17].

Cinnamaldehyde, a common cinnamon flavouring agent, is now known to be strongly cytotoxic and is thought to be associated with dysregulation of mitochondria and apoptosis. It can cause loss of ciliary movement in airway epithelial cells, thereby impairing mucosal ciliary transport [18]. Impairment of this key defence mechanism of the respiratory system may enhance the vulnerability to respiratory infections [18]. The reduction in ciliary motility is also thought to be associated with a transient decrease in ATP levels with the cell and a weakened bioenergetic activity [18]. Exposure to cinnamaldehyde has been found to impede the permeability of mitochondrial membranes and to reduce mitochondrial respiration [18]. The underlying cause of this effect may involve changes in key proteins within the mitochondria [18]. This could lead to significant effects on a variety of functions within the body, including those dependent on ATP, such as cilia, molecular motor proteins and  $Na^+/K^+$ -ATPase [18]. ATP can also act as a signalling molecule regulating various cellular processes by activating purinergic receptors, which include chloride channel regulation,  $Na^+$  uptake, mucin secretion and cerebral blood flow [18]. ATP is important in migration and repair of airway epithelial cell [18]. A decrease in intracellular ATP can disrupt these purinergic receptor-mediated functions [18].

It is interesting that the cytotoxicity studies on benzaldehyde are not as comprehensive as those on cinnamaldehyde. Although both benzaldehyde and cinnamaldehyde are used in food and medicine and both have anticancer effects, cinnamaldehyde is significantly more cytotoxic.

## 5. Conclusion

E-cigarettes have gained popularity as a replacement of traditional cigarettes, especially among young people. However, there are concerns about the potential health risks associated with inhaling e-cigarette aerosols, which contain a complex mixture of chemicals, including nicotine, flavourings and poisons. As a result, e-cigarettes have been linked to many cardiovascular diseases. Although many e-cigarette manufacturers claim that their products are harmless, scientific assessments suggest

that they are not completely risk-free. A systematic toxicological analysis of the chemicals commonly found in e-cigarettes. The focus was on nicotine, which is contained in both traditional tobacco and e-cigarettes, propylene glycol and vegetable glycerine, solvents in e-cigarette solutions, and benzaldehyde and cinnamaldehyde, common food flavouring agents. The chemical properties, toxicity and safety of these compounds are discussed in the hope of providing a comprehensive knowledge of any possible harms related to e-cigarette.

Nicotine is a highly addictive alkaloid that causes oxidative stress, neuronal apoptosis, DNA damage, and is highly toxic. E-cigarette solvents, such as vegetable glycerine and propylene glycol, can activate melanin production in the skin and enhance the chances of respiratory infection. Flavouring agents, benzaldehyde and cinnamaldehyde, have been found to cause cellular damage and increase the probability of diseases occurrence as cancer and cardiovascular disease, particularly in individuals with specific genetic variants of the ALDH2 enzyme. However, the current understanding of the effects of benzaldehyde on human health is ambiguous due to the lack of research in this area. There are stark differences in perceptions of the effects of benzaldehyde, with past perceptions of its toxicity to humans contrasting with the current discussion of its potential positive effects, such as its use as an anti-cancer drug. Additional investigation is required to thoroughly uncover the influence of benzaldehyde on human health, as well as to gain a deeper insight on the potential advantages and disadvantages associated of its use.

It is clear that there that current systematic evaluation of e-cigarettes is insufficient, indicating a need for more studies to comprehend the chronic health consequences of e-cigarette usage. And these studies should not only look at the ingredients of e-cigarettes alone, but also consider the potential products that may be produced. Various factors such as temperature and the proportion of ingredients should be considered. Despite the lack of research, the damage of some ingredients is known. Regulators must monitor the use and marketing of e-cigarettes on the market and should not conceal any potential harm to ensure the protection of consumer rights. Clinicians should also be aware of any adverse health outcomes of e-cigarettes and advise patients accordingly.

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