THE TURKISH JOURNAL ON ADDICTIONS
www.addicta.com.tr

INVITED REVIEW

The Use and Risks of Flavoring Agents in Electronic Cigarettes: Toxicological Approach

İsmet Çok

Department of Toxicology, Gazi University, Faculty of Pharmacy, Hipodrom, Ankara, Türkiye

ORCID iDs of the authors: İ.Ç. 0000-0003-3128-677X.

Main Points

- E-cigarettes are offered to consumers worldwide as an alternative to tobacco product to cigarettes, especially with the claim that users are exposed to fewer chemicals.
- E-cigarettes have been on the market for less than twenty years. Although the use of this product is rapidly increasing in all societies, scientific knowledge regarding the health risks that may arise from e-cigarette use is not increasing at the same pace.
- Today, the flavoring substances used in e-cigarettes play a vital role in the increase in e-cigarette use, particularly among young generations. There is extremely limited information about the chemical structures and toxicity of new compounds, especially those resulting from the combustion of flavorings.
- In vivo and in vitro toxicity results, in which toxic effects on lung functions have been reported with the use of flavored e-cigarette products, have shown that many serious health problems may occur due to flavorings.

Abstract

Because Electronic Nicotine Delivery Systems are fairly new, the information on the health risks of these systems is very limited; however, recent studies have provided results that show the harmful health effects of these products. Studies that have investigated the many chemicals in electronic cigarettes have reported a lesser ratio of harmful compounds in the vapor of e-cigarettes than that from regular cigarettes; however, it is misleading to claim no exposure to chemicals or carcinogens from electronic cigarette use for both the users and the public in terms of potential health risks. In fact, studies have found at least 20 human carcinogens and teratogens in the electronic liquids and vapor from these products. Chemicals used to flavor the products are among the main causes of harmful exposure, and their use is the leading cause of increased use of these products and plays an important role in creating a new epidemic health threat because of the lack of scientific data on the health risks of usage and exposure to various chemicals. The government and regulatory authorities have taken inadequate legal measures to limit the use of flavoring chemicals in these and tobacco products in general, which remains a public concern.

Keywords: ENDS, e-cigarette, flavoring, toxicity, toxic substances

Corresponding Author:
İsmet Çok
E-mail:
ismetc@gazi.edu.tr

Received: September 28, 2023
Accepted: December 11, 2023
Publication Date: XXXX XX, XXXX

Introduction

Many new products as alternatives to smoking have been introduced in response to record high numbers of smokers in recent years and increasing anti-smoking policies. The manufacturers of these new products hope to increase their market shares and revenues in response to these policies. The electronic cigarette (e-cigarette) is one of the most popular anti-smoking products in today's market, and the number of users is rapidly increasing throughout all populations but particularly in young people. In fact, of the more than 11 million e-cigarette users in just the United States, four million are middle school and high school students (Cullen et al., 2018). On the other hand, survey data reveal that the prevalence of electronic cigarettes among young people aged 11 – 18 years, which was 4.0% in 2021 and 4.8% in 2020, increased to 8.6% in 2022 in the UK (Limb,

Cite this article as:Çok, İ. (2023). The use and risks of flavoring agents in electronic cigarettes: Toxicological approach. *Addicta: The Turkish Journal on Addictions*, 10(3), 202-209.

DOI: 10.5152/ADDICTA.2023.23106

Table 1.
Flavored Electronic Cigarette Sales Volumes in the USA (2020 – 2022)

	Number of Sales (February 23, 2020)	Number of Sales (December 25, 2022)	Increase
Menthol	6 million	7.3 million	21.2%
Tobacco flavored	4.2 million	5.57 million	−1.0%
Mint flavored	0.8 million	1.4 million	61.5%
Other flavors	4.3 million	9.4 million	5117.8

2022). Today, it is reported that one in six Australians, a quarter of those aged 14 – 17, and a quarter of those aged 18 – 24, use e-cigarettes (Kirby, 2023). In China, another corner of the world, 86.6% of students in 2021 were aware of e-cigarettes. Of these, 3.6% were users (Deng et al., 2023). A study by the Global Adult Tobacco Survey conducted in 14 countries found that these figures are also common in Türkiye (Pan et al., 2022). In their study, Pan et al. (2022) have revealed that 1.3% of people in Turkey use e-cigarettes, which is 2.1% for men and 0.6% for women. These usage rates from various parts of the world reveal that the sales figures of e-cigarettes have increased worldwide. For example, between February 2020 (15.8 million units) and December 2022 (22.7 million units) in the USA, e-cigarette sales increased by 44% [Centers for Disease Control (CDC), 2022]. It is noteworthy that the products that have the largest share in these sales are flavored products. As a matter of fact, between 2020 and 2022, sales of non-tobacco flavored e-cigarettes (mint, menthol, and other flavors) increased from 11.1 to 18.0 million (61.6%) (Table 1).

Until a few years ago, one or more of the following purposes were reported by users for Electronic Nicotine Delivery System (ENDS) use (Göney et al., 2016): a) reducing cigarette consumption, b) not disturbing others with cigarette smoke, c) helping with smoking cessation, d) continuing the "smoking" experience even where prohibited, e) presumed exposure to lower amounts of toxic chemicals to reduce health risks, f) having nicotine replacement therapy, and g) spending less money. However, many of these reasons stand before us as refuted reasons today. For example, the rate of tobacco use increases in e-cigarette users, with some using both cigarettes and e-cigarettes, and there is a return to smoking again. Although less exposure to chemicals and concentrations due to e-cigarette use is a fact, many studies have been published showing that the number and variety of chemicals exposed to are increasing day by day; therefore, it is misleading to suggest that users and the public are not being exposed to chemicals or carcinogenic substances and their health risks from e-cigarette use. As a matter of fact, scientific studies have determined at least 20 human carcinogens and teratogens in the liquids used in e-cigarettes and e-cigarette smoke. On the other hand, the World Health Organization completely rejects the idea that e-cigarette use should replace replacement therapy. In recent years, e-cigarette users have indicated that the various flavors in the products are the main reasons for their starting e-cigarette use. They report that the attractive flavors of e-cigarettes are the most essential reason for e-cigarette users to try these products (Baker et al., 2021; Landry et al., 2019).

There are significant differences between smoking and e-cigarette use (Gordon et al., 2022). Although a cigarette is a combustion product, e-cigarettes involve the intake of aerosolized liquid into the body. First, although more is needed, there are enough legal regulations in almost many societies for cigarettes. However, the number of legal regulations regarding e-cigarettes in all countries is relatively low. Cigarette is not a product that has the chance to be "individualized/customized"; it is in question for smokers to use the product as it is presented. On the other hand, e-cigarettes have adjustable settings (e.g., wattage, voltage, resistance, airflow) so that they can be customized to the user to increase the experience. Another important difference is the many flavorings used in ENDS. Both of these factors play a role in increasing e-cigarette use, especially among young people.

Tobacco smoke can be harsh and irritating and provides an important obstacle against continued use after first trying. In the tobacco industry documents, it is seen that this negative situation is tried to be alleviated especially by sweeteners, sugar, and various chemicals used to increase tobacco flavor. "Characterizing flavor" or "characterizing flavor combinations" that are added to e-cigarette liquids, such as fruit, spice, herb, and alcohol, mask the bitter taste of cigarette smoke and provide a more appealing taste. For example, the combustion of sugars creates caramel flavors in tobacco smoke, which gives the product a sweet taste that is especially appreciated by adolescents (Talhout et al., 2006). Menthol provides taste and a physiological "cooling" effect. When added in sufficient quantities, they change the flavor of the product into a strong, non-tobacco flavor such as menthol, fruit, or sugar. Such strong flavors are popular with young smokers (Yerger & McCandless, 2011). Today, more than 15,000 different flavored e-liquids are sold in the United States (Salam et al., 2020), and 28,556 e-liquids were registered for the Dutch market (Pennings et al., 2023). Although there is no clear classification for flavorings generally used in e-cigarette liquids, there are various suggestions for classification. For example, an e-liquid flavor wheel consisting of 16 main categories was created by Krüsemann et al. (2019) and was based on information from four variables in the European Union Common Entry Gate system with subcategories of flavor descriptions.

In fact, the chemicals enable the classification and subgrouping of flavorings. E-cigarette users get different flavors due to the different flavoring chemicals contained in e-liquids. For example, it is known that there are four different chemicals (vanillin, maltol, ethyl vanillin, ethyl maltol) in the flavoring called "Double Dark Chocolate." Another example is the flavoring named "Grape," where five different chemicals form the flavor of this product (maltol, ethyl acetate, ethyl maltol, methyl anthranilate, and ethyl isovalorate). These chemicals are included in e-cigarette liquids alone or in combinations. It is these flavoring chemicals that make the most important contribution to e-cigarettes becoming an important public health problem in societies today. Flavor is a critical component that appeals to users of e-cigarettes, with sweet flavors not only increasing their use but providing more satisfaction and pleasure. Studies have suggested that sweet and menthol/mint flavors increase e-cigarette appeal. The high

market sales of e-liquids or disposable pots containing sweet and menthol/mint flavors are evident from the high market availability and sales graphics, with US ENDS users largely favoring menthol, mint, and sweet flavors; however, preferences can vary based on the age, smoking status, and sex of the user and the type of device used. In fact, the results of a 2020 – 2021 US study by the National Youth Tobacco Survey with a large participation of young population determined that flavorings are highly accepted and preferred (Cooper et al., 2022). The study also showed that fruit, candy, desserts, and other sweet flavors were the most commonly used flavor types, especially among adolescent e-cigarette users.

We do not have enough information about the health risks posed by the chemicals that make up the flavorings. We also have very limited information about the toxicological risks that may arise due to the combustion and inhalation of these chemicals. Depending on the increase in the number of health risks, national and international regulatory institutions have also started to need to take some precautions. Although the history of e-cigarette use does not last very long, regulations in countries have started to develop rapidly. For example, in February 2020, the U.S. Food and Drug Administration (FDA) issued an enforcement policy that prohibits the sale of prefilled flavored e-cigarette cartridges; however, this policy does not apply to tobacco and menthol-flavored prefilled cartridges, e-liquids, or single-use disposable e-cigarettes. Subsequently, from February 23 to December 25, 2022, disposable e-cigarette sales increased from 4.9 to 11.8 million units (139.9%); their unit share increased from 31.1 to 51.8% of total e-cigarette sales (CDC, 2022). As of December 25, 2022, 80.0% of disposable sales comprised flavors other than tobacco, mint, and menthol. In addition, as of September 9, 2021, FDA began issuing marketing rejection orders for flavored e-cigarette products, and by April 15, 2022, it was given authority to regulate products containing nicotine, including synthetic nicotine, from any source. Finally, in April 2022, FDA issued a proposal to eliminate both menthol cigarettes and flavored cigars. On the other hand, Article 7 of EU Directive 2014/40/EU (European Parliament and of the Council, 2014) prohibits placing tobacco products with a distinctive flavor on the market. The Commission Implementing Regulation (EU) 2016/779 has created rules for procedures used to determine whether a tobacco product has a characterizing flavor. According to the European Tobacco Products Directive, before launching their products, e-cigarette and e-liquid manufacturers are required to provide basic product information about the brands and compositions of their products to the authorities of the 27 EU member states; however, practices in the EU differ. For example, Hungary bans all flavorings in ENDS products, while Finland and Estonia ban e-cigarette products containing flavors other than tobacco, and Denmark prohibits vaping products containing flavors other than tobacco or menthol. The Dutch government has announced that a restrictive list of flavor-determining additives in e-cigarettes will be created based on data manufacturers report through the European Common Gateway of Entry (EU-CEG) system (Pennings et al., 2023). Within the framework of the values obtained from the 2019 EU-CEG data set, it was determined that the top five sweeteners most frequently added to e-liquids are vanillin, maltol, ethyl maltol, ethyl acetate, and ethyl butyrate (Krüsemann et al., 2021).

Concerns About Flavorings Used in E-Cigarettes

Young people come first in our concerns about e-cigarettes. One study has shown that younger smokers are up to three times more likely to try flavored cigarettes than older, established smokers (Ashare et al., 2007). In particular, the first product used by young people in tobacco products was a flavored product (Ambrose et al., 2015). Most teens who use e-cigarettes have indicated that they started with a flavored variety. Early use as a teen or young adult increases the likelihood of smoking tobacco products. In addition, it has been determined that users of flavored e-cigarettes are less likely to quit using e-cigarettes or tobacco products (Dai &Hao, 2016). Of young e-cigarette users, 81.5% who participated in the 2013 – 2014 Population Assessment of Tobacco and Health study have stated that they use e-cigarettes "because they have the flavors they like" (Ambrose et al., 2015). It shows that flavors also contribute to the innovation of e-cigarette devices, which are called "fun toys" that young people keep with them after mobile phones. As a matter of fact, the USA 2022 National Youth Tobacco Survey determined tobacco product use was 2.14 million (14.1%) for high school students and 380,000 (3.3%) for middle school students. One of the important results of this research is that e-cigarettes are currently the most widely used tobacco product by 1.72 million (11.3%) of high school students and 320,000 (2.8%) of secondary school students (Park-Lee et al., 2022). In addition, 84.9% of the participants in this study who use tobacco products have reported that they use flavored products, which reveals the importance of flavors in tobacco addiction.

Although some flavorings used in e-cigarette liquids are flavorings used in foods, there is little information about the toxicity profiles that may occur, especially the genotoxic effects of many of them and their mixtures. In addition, there is little information about the chemical structures of new products formed by flavorings after combustion. Moreover, little is known about the toxicity of newly formed compounds from flavorings. Another essential concern is that the doses of flavorings used in e-cigarette products are not the same and show great fluctuations, as this situation may cause differentiation and change in the toxic effects that may arise. In addition, the fact that we need in-depth scientific knowledge about the new components to be sourced from flavorings due to heating and how their structures affect the e-liquid content is another of our concerns in this regard.

Apart from the abovementioned, besides the known food additives, e-liquids can also contain natural extracts, such as tobacco, essential oils, plants, or other additives, that are not chemically synthesized. The composition of these natural extracts can vary depending on the biological and geographical origins; therefore, it is highly likely that e-liquids and/or e-cigarette emissions contain substances of known or unknown toxicological properties that exceed the allowed exposure limits and cause acute and/or chronic adverse effects on health.

In order to minimize health risk concerns in their products, e-cigarette manufacturers choose all flavorings used in their products listed as "food grade" and "generally recognized as safe" (GRAS) substances. In fact, GRAS values are valid for specific purposes and specific foods at specific concentrations and not for inhalation. The Flavor Extracts Manufacturers Association (FEMA) states that "GRAS certification is only for oral intake,

not inhalation, and does not evaluate flavoring ingredients used in e-cigarettes or non-human food products" (Flavor and Extract Manufacturers Association, 2013).

Electronic Cigarette Flavoring and Health Effects

In a study conducted in nine European Union countries in 2016, 171 different flavorings were found in 122 e-liquids. It was determined that 41 of these chemicals were recorded with the "warning" code by the Globally Harmonized System of Classification and Labeling of Chemicals and 11 with a "danger code." It was determined that nine of these chemicals were recorded with both codes (Girvalaki et al., 2018). The meaning to emerge from this situation is that toxicological warnings are placed on flavoring substances before they are used, and the first warnings for users about the health risks that may occur are started to be presented on their labels before use.

The most common and major health problem experienced due to e-cigarette use until today is the health problem called e-cigarette and vaping use associated with lung injury (EVALI), which has resulted in the death of many people in the United States. EVALI is an acute or subacute lung injury ranging from mild respiratory symptoms to severe lung issues, such as diffuse alveolar hemorrhage, lipoid pneumonia, acute eosinophilic pneumonia, and diffuse alveolar damage. As of February 18, 2020, 2807 EVALI patients had been reported to the CDC, of which 68 had died. E-cigarette and vaping use associated with lung injury is most often associated with the use of cannabis-based vaping products, particularly vitamin E acetate, which is found in some tetrahydrocannabinol-containing e-cigarette products (CDC, 2020). Çok et al. (2021) have found similar clinical and radiographical findings in patients with coronavirus disease 2019.

One of the areas where human data are obtained when evaluating the toxicities of chemicals is the toxicity results from exposure in the workplace. Diacetyl and acetyl propionyl, which are especially used in the food industry and used to provide buttery flavor, are also used as synthetic flavorings in e-liquids. It has been determined that adverse effects on respiratory epithelial cells occur due to the exposure of people working in food-related workplaces where these compounds are used. It has been determined that it causes a decrease in lung capacity (decreased FEV1 (i.e., forced expiratory volume in the first second of expiration)) in exposed people and that some people develop bronchiolitis obliterans, also known as "popcorn lung," which is a fatal condition (Farsalinos et al., 2015). Similar clinical findings were also supported by experimental animal studies. The use of these substances as flavoring in e-cigarette liquids poses a risk of serious respiratory problems in e-cigarette users flavored with these substances since the aerosol of e-cigarettes is taken directly into the lungs.

One of the parameters used when risk assessment of exposure to genotoxic and carcinogenic substances in toxicological studies is the risk assessment parameter called margin of exposure (MOE). Margin of exposure is the evaluation parameter that regulatory agencies use when assessing food additives for cancer risks. This value is obtained by dividing the dose value at which no adverse effects were observed by the exposure dose

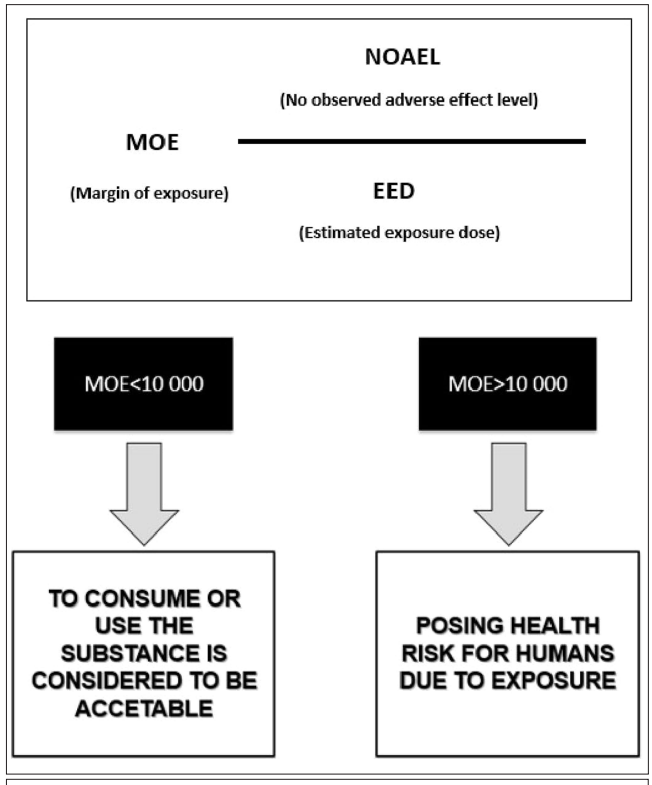
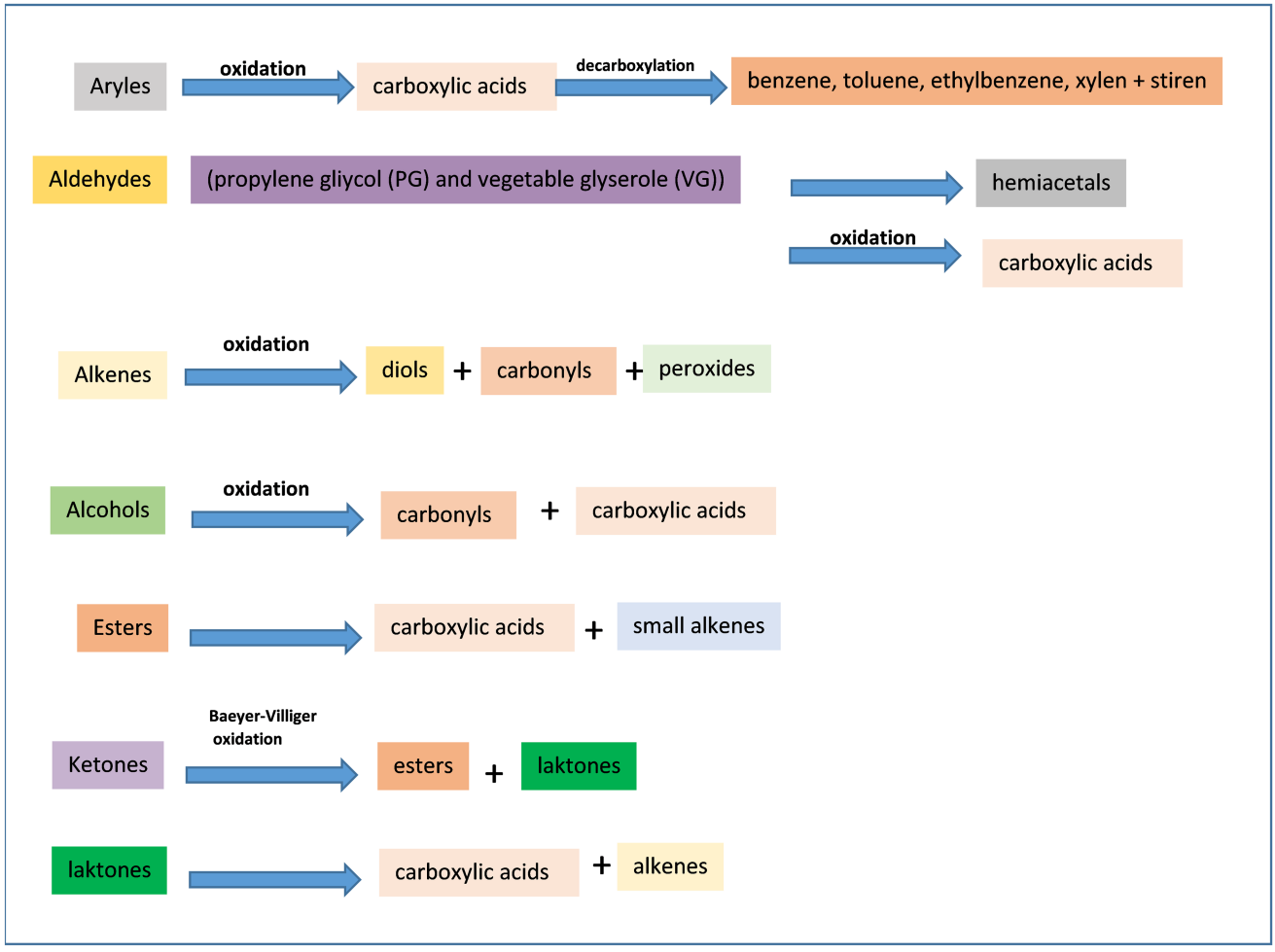


Figure 1. Margin of exposure approach for risk assessment.

received. If the value received is higher than 10,000, it indicates that the compound exposed is not a risky compound in terms of genotoxicity. If the value is less than 10,000, it is accepted as an indication that the compound carries a risk of genotoxicity for humans (Figure 1). In a study conducted by the CDC on menthol cigarettes, e-liquids containing menthol and mint flavor, and smokeless tobacco products flavored with menthol and mint, it was determined that other products except cigarettes contained pulegone well below the MOE value (Jabba & Jordt, 2019). Pulegone, a component of oil extracts prepared from peppermint plants, is a carcinogenic substance that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms in experimental animals. Synthetic pulegone as a food additive was banned by the FDA in 2018; however, menthol- and mint-flavored e-cigarettes may be exempt from these FDA regulations. Thus, considering the health risk associated with pulegone, more encompassing regulations are needed to prevent these products from posing a health risk.

Various reactions, such as oxidation and thermal decomposition, radical generation/addition, and formation of adducts, and the formation of new products can occur during e-cigarette use (Salam et al., 2020; Qu et al., 2018). The use of flavorings in e-cigarettes in the form of many chemical groups causes the formation of plenty of new compounds from these chemicals, primarily due to oxidation and heat. Data on both chemical structure and toxicological evaluations of these compounds are extremely scarce. However, in general, volatile organic compounds such as carbonyls, carboxylic acids, alkenes, and BTEX (benzene, toluene, ethylbenzene, xylene), and styrene appear in e-cigarette vapor due to heating. In other words, heating e-cigarette liquids and flavorings added to these liquids can cause the formation of new

Table 2.
Summary of Predicted Chemical Transformation of Flavoring Agents



toxic compounds (Table 2). For example, benzene, a toxic-carcinogenic compound, is released due to dehydration of glycerol and propylene glycol in e-cigarette liquids (Pankow et al., 2017). Benzene can also be formed by the oxidation of benzaldehyde, a flavoring substance used to give fruit flavor, especially cherry, due to its addition in e-liquid. It has been determined that the amount of benzene increases depending on the increase in power in e-cigarette devices whose power can be adjusted today. This results in such users having an increased risk of cancer. Another example can be given for ethyl ester flavor additives. Among them, ethyl acetate and ethyl butyrate stand out as the most commonly used flavors. These two ethyl ester flavoring additives are popular with manufacturers because of their low price and favorable solubility in propylene glycol. Carboxylic acid and ethene are formed from these flavorings at high temperatures. Acetic, propionic, and butanoic acids, which are formed at even higher temperatures, have the potential to cause lung irritation at low doses and cause bronchitis with repeated exposure. In more extreme operating conditions, repeated exposure can cause fatal or seriously harmful effects both from these substances and from the ketene formed. These high temperatures can be reached in "dry" operating conditions resulting from improper use, especially in user-modified electronic cigarettes such as Mods (Narimani et al., 2022).

For example, 2-methylbutyraldehyde added to e-liquid to create a chocolate taste turns into formaldehyde when heated to 200°C. Use of e-cigarettes can also emit toxic aldehydes from the added flavorings in the e-liquids (Klager et al., 2017). So far, aldehyde formation due to e-cigarette use has been attributed to the thermal decomposition of the main components of e-liquids (propylene glycol and glycerol); however, the role of flavor compounds in the formation of these aldehydes has been ignored. In a study to determine the presence of aldehydes from flavorings, concentrations of some toxic aldehydes produced in flavored and unflavored e-liquids were measured by three popular e-cigarette brands. It has been determined that toxic aldehyde levels formed due to thermal decomposition of flavoring compounds are quite high, especially during the smoking of e-cigarettes containing flavorings. The American Conference of Governmental Industrial Hygienists has reported that levels of formaldehyde and acrolein from flavored e-cigarette use exceeded occupational safety standards (threshold limit value (TLV)—ceiling) for workers at their workplaces (Khlystov & Samburova, 2016). Formaldehyde is one of the human carcinogens evaluated by the International Agency for Research on Cancer (IARC) (Prrotano et al., 2021). Acrolein, which is formed from formaldehyde due to heat, is a carcinogen classified in Group 2A (probably carcinogenic) by IARC (IARC 2021) (Figure 2).

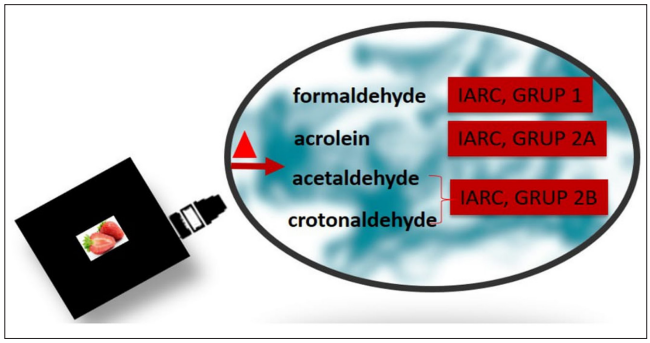


Figure 2. Carcinogenic evaluations of some aldehydes originates from e-cigarette use.

When it comes to the effects caused by the flavorings and the new chemicals formed due to the use of e-cigarettes, the first thing that comes to mind is the toxic effects of the lungs, which are the organs where the exposure is intense, and the cells therein. However, current in vitro and in vivo animal studies can help predict the potential effects of flavors on the human respiratory system, as they provide information on the toxicity attributed to cinnamon, strawberry, menthol, and other flavorings (Effah et al., 2022). In vitro studies in mouse lung cells have shown that inhalation exposure to sweeteners has been associated with decreased pulmonary cell proliferation, decreased cell viability, increased cytotoxicity, increased oxidative stress from increased reactive oxygen species (ROS) and reactive nitrogen species (RNS), DNA damage, increased inflammatory cytokines, epithelial barrier dysfunction, changes in cilia frequency, mitochondrial dysfunctions, and cellular senescence. In addition, the presence of ROS that cause cellular senescence and DNA damage have also been demonstrated in vitro in experimental animal studies (Kaur et al., 2018). Flavorings in e-liquids have also been shown to cause hypersensitivity to the peripheral airway, damage to lung tissue, pre-pregnancy exposures, lung tissue fraction increases at birth, increases in MUC5A, oxidative stress, and bronchoalveolar lavage cellularity in rodents in vivo. It has been previously determined that cigarette smoke contains high levels of free radicals ($>10^{16}$ molecules/puff). Similarly, e-cigarette aerosols also contain high concentrations of reactive free radicals ($>10^{13}$ molecules/puff). The presence of free radicals such as ROS and RNS in e-cigarette aerosols results in the induction of oxidative stress that damages the cell proliferation, survival, and inflammation pathways (Bitzer et al., 2018). Oxidative stress, barrier dysfunction, and inflammation in monocytes and lung epithelial cells induced by flavored e-cigarettes with various flavorings were evaluated. For this purpose, JUUL pod flavors (Virginia Tobacco, Fruit Medley, Cool Cucumber, Crème Brulee, Cool Mint, Mango, and Classic Menthol) and similar pod flavors (Just Mango-Strawberry Coconut and Café Latte) were tested by Muthumalage et al. (2019). These pod flavors have been found to produce significant amounts of acellular ROS and induce significant mitochondrial superoxide production in bronchial epithelial cells (16-HBE). In addition, levels of inflammatory mediators such as interleukin 8 (IL-8) or PGE2 were found to be increased in the lung epithelial cells (16-HBE, BEAS-2B) and monocytes (U937) that were exposed to various pod aerosols. Exposure to the sweeteners Crème Brulee and Cool Cucumber aerosols induced epithelial barrier dysfunction in 16-HBE cells. Also, flavored pots tested with the help of the comet assay test were shown in this study to cause DNA damage in monocytes due to exposure. Due to the increasing number of similar studies, the CDC has suggested that vaping-related lung injury may occur (Siegel et al., 2019).

In their study on human venous endothelial cells, Fetterman et al. (2018) have examined the effects of flavorings on the cardiovascular system. Nine flavorings (eugenol, diacetyl, menthol, cinnamaldehyde, vanillin, dimethylpyrazine, acetylpyrazine, eucalyptol, and isoamyl acetate) were examined for their effects on venous endothelial cells isolated from nonsmokers, non-menthol cigarette smokers, and menthol cigarette smokers without cardiovascular disease. Although A23187-stimulated nitric oxide production was more impaired in the endothelial cells isolated from the smokers of menthol or non-menthol-flavored tobacco than those from nonsmoking participants, treatment with menthol or eugenol of endothelial cells isolated from nonsmokers also revealed reduced A23187-induced nitric oxide production. On the other hand, cell death, production of ROS, expression of proinflammatory marker IL-6, and nitric oxide production in endothelial cells were evaluated in the exposure of human aortic endothelial cells to these nine flavorants. As a result of this evaluation, it was determined that cell death and production of ROS were induced only at high levels that are unlikely to be achieved in vivo. Lower concentrations of vanillin, menthol, cinnamaldehyde, eugenol, and acetylpyrazine have been found to both induce inflammation and impair A23187-stimulated nitric oxide production, consistent with endothelial dysfunction. These results have been interpreted by researchers as that short-term exposure of endothelial cells to flavoring compounds used in tobacco products may cause adverse effects on the endothelial cell phenotype related to cardiovascular toxicity (Fetterman et al., 2018).

New information, but only a small volume, has begun to emerge in the scientific world about the hepatotoxic effects of flavorings on the liver from e-cigarette use. For example, in an in vivo study to evaluate the effects on the liver of ethyl maltol, vanillin, ethyl vanillin, L-menthol, trans-cinnamaldehyde, and isoamyl acetate e-cigarette flavors, human liver cancer cell line (HepG2) cells were exposed to flavoring chemicals, propylene glycol, and vegetable glycerin mixtures to measure their viability. Study results have revealed that cell viability decreased when exposed to vanillin, ethyl vanillin, and ethyl maltol. In addition, repeated exposure caused greater cytotoxicity than a single exposure. While these data also provide new information on how e-cigarette vaping and flavors can cause hepatotoxicity, it is also a pioneering study that guides further studies on this subject (Rickard et al., 2021).

Conclusion

Believing that the use of e-cigarettes is safer than smoking tobacco puts our youth on a path that threatens their health and future. Unfortunately, the increasing use of e-cigarettes has become a worldwide public health concern. The presence of a large number of e-cigarette users, although its sale is prohibited in our country, also reveals the unexplained dimensions of this problem that threatens society. It is a fact that the scientific world agrees that the flavorings used in e-cigarettes play a major role in the increased e-cigarette use worldwide. The legal regulations for flavorings used in tobacco products should include e-cigarettes,

and new regulations that ban or limit flavorings, could reduce e-cigarette use and exposure to potentially toxic e-liquid components. It is necessary to establish national scientific commissions that will evaluate the differences in the use of chemicals, such as flavoring chemicals used in both food and tobacco products, their restrictions in different products, new chemical products, and their toxicities due to the way they are used.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – I.C.; Literature Search – I.C.; Writing – I.C.; Critical Review – I.C.

Acknowledgment: The author would like to thank GAZİ University's Academic Writing Application and Research Center for proofreading the article.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: The authors declare that this study has received no financial support.

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Genişletilmiş Özet

Giriş

Elektronik Nikotin Dağıtım Sistemleri (ENDS) oldukça yeni olduğundan, bu sistemlerin sağlık risklerine ilişkin bilgiler çok sınırlıdır; ancak son zamanlarda yapılan araştırmalar bu ürünlerin sağlığa zararlı etkilerini gösteren sonuçlar ortaya koymuştur. E-sigaradaki birçok kimyasalın araştırıldığı çalışmalar, e-sigara buharında normal sigaraya göre daha az zararlı bileşik oranının olduğunu bildirmiştir; ancak potansiyel sağlık riskleri açısından e-sigara kullanımından dolayı hem kullanıcıların hem de halkın kimyasallara veya kanserojenlere maruz kalmadığını iddia etmek yanıltıcıdır. Aslında çalışmalar, e-sıvılarda ve bu ürünlerden çıkan buharda en az 20 insan kanserojeni ve teratojeni tespit etmişlerdir. E-sigara Ürünlerini tatlandırmak için kullanılan kimyasallar, zararlı maruziyetin ana nedenleri arasında yer almakta olup bunların kullanımı, bu ürünlerin kullanımının artmasının ana nedeni olup, bu ürünlerin kullanılması ve çeşitli kimyasallara maruz kalma sağlık riskleri konusunda bilimsel veri eksikliği nedeniyle yeni bir salgın sağlık tehdidi oluşturulmasında önemli bir rol oynamaktadır.

E-sıvılarda kullanılan çok sayıda katkı maddesi göz önüne alındığında, bunların her birinin güvenliğinin inhalasyon yoluyla değerlendirilmesi oldukça zordur. Şu anda e-sıvı toksisitesi hakkında yalnızca çok sınırlı bilgi mevcuttur. Aslında, çalışmalar şimdiye kadar esas olarak yüksek verimli hücre canlılığı analizlerinin gerçekleştiği in vitro sitotoksisite testlerine odaklanmış olup, bu çalışmalarda da e-sıvı, propilen glikol ve gliserol çözücüleri ile kombinasyon halinde farklı aroma verici maddeler tam bir karışımı olarak test edilmektedir.

Son yıllarda e-sigara kullanıcıları, e-sigaraya başlamalarının/denemelerini genellikle e-sigaraların içerdiği binlerce "tat" ile ilişkilendirip, birincil nedeni olarak; e-sigaraların çekici aromalara sahip olması özelliğini göstermektedir. Bugün için ABD pazarında >15,000 ve Hollanda pazarında >20,000 fazla farklı aromalı e-sıvı satılmaktadır. E-sigara sıvılarına ürünün tadını değiştirmek amacıyla meyve, baharat, bitki, alkol dahil ancak bunlarla sınırlı olmamak üzere katılan "karakterize edici tat," veya "karakterize edici tat kombinasyonları" toplu olarak "aroma vericiler" olarak anılır. Aromalı tütün ürünlerinin, tütün ürünleri kullananların çoğunda özellikle de gençlerin kullandığı ilk ürünün aromalı bir ürün olduğunu belirlenmiştir. Nitekim günümüz çalışmaları e-sigara kullanan çoğu gencin ilk önce aromalı bir çeşitle e-sigaraya başladığını bildirmektedir. Ayrıca ergenlik veya yetişkinlikte e-sigara kullanımına başlamanın daha sonra yanıcı sigara kullanma olasılığını artırdığını da saptanmıştır. Tüketimi teşvik etmek, ürünü daha cazip hale getirmek için eklenen en yaygın tatlar, naneli, tatlı, meyveli, biberli ve tereyağlı tatlar gibi çok çeşitli seçeneklere ulaşmaktadır. Aroma vericiler çoğunlukla e-sıvıların içine ilave edilmektedirler. Bu amaçla, benzaldehit, sinnamaldehit, sitral, etil vanilin ve vanilin dahil olmak üzere çok sayıda kimyasal madde tek başına veya karışım halinde e-sıvı matrislerine katılmaktadır.

Sağlık riskleri

Aroma verici kimyasallar, ENDS'e sürekli olarak eklenen ve ürünleri tüketiciler için daha çekici hale getirmek amacıyla kullanılan kimyasal maddelerdir. Her ne kadar ENDS'ye eklenen aroma verici kimyasalların birçoğu, ABD Aroma ve Ekstrakt Üreticileri Birliği tarafından 'genel olarak güvenli '" (GRAS) kabul edilse de, bu bileşikler yutma için güvenli olup, ısıtıldıktan sonra solunması için güvenli değildir. Ağızdan tüketim için güvenlik açısından onaylanan bazı ayrıcalıkların, e-sigara içimi yoluyla solunduğunda potansiyel olarak toksik olduğuna dair göstergeler vardır. Ağızdan kullanım için güvenli olan, ancak akut ve kronik maruz kalma sonrasında lokal akciğer iltihabına neden olan aroma vericilerin en iyi bilinen örneği, diasetil ve asetilpropiyonil diketonlardır. Ayrıca e-sıvılarda bilinen gıda katkı maddelerinin yanı sıra tütün ekstraktları, esansiyel yağlar, bitkisel ekstraktlar gibi doğal ekstraktlar veya kimyasal olarak sentezlenmemiş katkı maddeleri de mevcut olabilir. Bu ekstraktların bileşimi genellikle iyi bilinmemektedir ve biyolojik ve coğrafi kökenlere bağlı olarak partiden partiye değişiklik gösterebilir. Bu nedenle, e-sıvıların ve/veya e-sigara emisyonlarının, bilinmeyen toksikolojik özelliklere sahip maddeler veya belirli sınırları aşan bilinen toksik bileşenler içermesi ve dolayısıyla insan sağlığı üzerinde akut ve/veya kronik olumsuz etkilere neden olması kuvvetle muhtemeldir.

Solunuma kadar uzanan süreçler, aroma verici bileşiklerinden ultra ince parçacıkların yanısıra yanmaya bağlı çeşitli kompozisyonlarda yeni bileşiklerin oluşmasına neden olur ki bunların çoğu hakkında yapısal ve toksikolojik bilgi eksikliği söz konusudur. Daha da zorlu olanı, üretilen e-sigara aerosol emisyonlarında (ısıtma ve etkileşim ürünleri) bulunan kimyasalların tanımlanması ve değerlendirilmesidir. Nitekim bazı çalışmalarca e-sigara dumanında aroma vericilere bağlı olarak oluşan toksik aldehitler ile e-sıvılardaki katkı maddeleri miktarı arasında bir korelasyon bulunmuştur. Ayrıca aerosol emisyonlarında, farklı maddeler arasındaki reaksiyonlar nedeniyle ısıtma ürünlerinin yanı sıra etkileşim ürünleri de bulunabileceği unutulmamalıdır. Oluşan bu yeni bileşiklerin akciğerler tarafından emilimi sonucu doğrudan zararlı sistemik etkilerin ortaya çıkması kaçınılmazdır. Aroma vericilerin ürünlerdeki dozları aynı olmayıp büyük farklılıklar göstermektedir. Bu durum ortaya çıkabilecek toksik etkilerin farklılaşması ve değişmesine neden olabilir.

Bununla birlikte, kimyasalların e-sigara yoluyla kasıtlı olarak solunması, 2019'da ABD'de, 68 kişinin ölümüyle sonuçlanan, e-sigara veya elektronik sigara ürünü kullanımıyla ilişkili akciğer hasarı (EVALI) vakasının ortaya çıkmasıyla gösterildiği gibi, risksiz değildir. Özellikle aldehit gruplarından gelen maddeler solunum yollarının lokal tahriş edicileri olarak bilinmektedir. Bu nedenle, e-sıvıların ve/veya e-sigara emisyonlarının, bilinmeyen toksikolojik özelliklere sahip maddeler veya belirli sınırları aşan bilinen toksik bileşenler

içermesi ve dolayısıyla insan sağlığı üzerinde akut ve/veya kronik olumsuz etkilere neden olması kuvvetle muhtemeldir. Son araştırmalar, e-sıvıların safrol, estragol, 2-furil metil keton, dimetilhidroksifuranon ve pulegon gibi genotoksik bileşenler içerebileceğini göstermiştir.

Tartışma ve Sonuç

Açıkçası, toksikolojik bilgi eksikliği, e-sigara aerosollerinin, bu aeresollerde e-sıvı içine katılan aroma verici maddeler gibi katkı maddelerinde kaynaklanan ısıtma/etkileşim ürünleri de dahil olmak üzere derinlemesine analizini gerektirmektedir. Diğer yandan e-sigaralar ve e-sigaralarda kullanılan aroma verici maddelere yönelik hükümetler ve düzenleyici makamlar günümüze kadar, bu ürünlerde ve genel olarak tütün ürünlerinde aroma verici kimyasalların kullanımını sınırlamak için yetersiz yasal önlemler almıştır ve bu durum kamuoyunu endişelendirmeye devam etmektedir. Ayrıca aroma kullanımın yasaklanması veya kullanım konsantrasyonlarının kısıtlanması, e-sigara kullanımın azalmasına ve potansiyel olarak toksik e-sıvı bileşenlerine maruz kalmayı azaltmada önemli rol oynayacak faktör olarak görülmektedir