Eurasian J Pulmonol 2017; 19: 1-7

Electronic Cigarette (E-Cigarette) Using: Toxicological Aspects

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Abstract

The use of electronic cigarettes (e-cigarettes) has increased dramatically over the past few years. Moreover, no sufficient scientific evidence is available confirming the safety, efficacy also toxicity of e-cigarette's. The aim of this review is evaluate and giving information about the toxic effects of e-cigarette's using and its chemicals.

Keywords: E-cigarette, electronic cigarette, electronic nicotine delivery systems, vaping

INTRODUCTION

Electronic nicotine delivery systems (ENDS), which can be as also called "personal vaporizer", "vape pen", "e-waterpipe", or "e-cigarette", have become increasingly popular in recent years (1). The supporters of ENDS argue that the users are exposed to lesser chemicals, and these systems help quit smoking, and thus, ENDSs are safer than cigarettes (2). E-cigarette is a product that looks like a cigarette, gives a cigarette-like feeling, but unlike cigarettes, it does not burn tobacco. E-cigarettes are devices that consist of a solution of nicotine and other flavors (such as chocolate, coffee, mint, or fruity tobacco varieties) in a liquid containing propylene glycol (PG) and/or vegetable glycerol and a battery is used to evaporate this liquid mixture. While smoking, an apparent vapor comes into view, but it is not like the usual cigarette smoke (3). Analyses made by the Food and Drug Administration (FDA) have shown that e-cigarette contains carcinogens such as nitrosamines, diethylene glycol, and tobacco-specific compounds, such as anabasine, myosmine, and β-nicotin, which can be harmful to humans. In addition to the FDA report, some researchers have reported that e-cigarette smoke may contain metals such as mercury in addition to volatile compounds such as acetaldehyde. World Health Organization (WHO) reports that there is no scientific evidence confirming the effect and safety of e-cigarettes (4, 5). Despite the studies comparing the toxic compounds contained in the smoke of cigarette and e-cigarette (6, 7), the number of studies on e-cigarette and its effects on human health is rather limited, as it is new. In a study from Germany, due to the use of e-cigarette in closed-area emissions, volatile organic chemicals, such as 1,2-propanediol and nicotine, and fragrant substances were detected (8). The results of the study have shown that e-cigarette may contain the same toxic and carcinogenic compounds as the conventional cigarettes such as polycyclic aromatic hydrocarbons (PAH), diethylene glycol, and nitrosamines (Tables 1, 2).

Potential health risks of the chemicals contained in e-cigarettes

E-cigarette is suggested to be a more reliable alternative in comparison to the conventional cigarette (10). Researches have been made to determine the threshold limit value (TLV) for e-cigarette and the toxicity risks related to the usage at work places. When compared with smoke from cigarettes, harmful compounds were found to be 9 to 450 times less in smoke from e-cigarette (Table 3) (11). Since e-cigarette smoke remains in the air for a short time, the risk of passive exposure is greatly reduced. For this

Received Date: 20.07.2016
Accepted Date: 29.09.2016

DOI: 10.5152/ejp.2016.49358

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• Available online at www.eurasianjpulmonol.com

Table 1. Content and quantity of the chemical substances in e-cigarette cartridge (9)

Chemical content in the cartridge (mg)	Nicotine content in cartridges			
	16 mg	11 mg	6 mg	0 mg
Water	40	40	40	40
Alcohol	50	50	50	50
PG	888	893	898	904
Nicotine	16	11	6	0
Flavor	6	6	6	6
Total (mg)	1,000	1,000	1,000	1,000

PG: Propylene glycol

Table 2. Substances and quantities found in the smoke of an example e-cigarette (9)

Compound	Average (ppm)
Acetaldehyde	0.34
Acetone	0.16
Ethanol	100
Formaldehyde	0.25
Cresol	0.16
Xylene	0.18
PG	32
Styrene	0.29

*The detection limit for this study is 0.01 ppm and the quantification limit is 0.025 ppm
PG: Propylene glycol

Table 3. Hazardous compounds in electronic cigarette aerosol and cigarette smoke (11)

Substance	Cigarette (µg, smoke)	E-cigarette (at 15 times inhalation/µg)	Average in e-cigarette
Formaldehyde	1.6-52	0.20-5.61	9 times less
Acetaldehyde	52-140	0.11-1.36	450 times less
Acrolein	2.4-62	0.07-4.19	15 times less
Toluene	8.3-70	0.02-0.63	120 times less
N'-nitrosonornicotine	0.005-0.19	0.00008-0.00043	380 times less
N'-nitrosonornicotine and 4 (diethylnitrosamine)-1-(3-pyridyl) -1-butanone	0.012-0.11	0.00011-0.00283	40 times less

reason, it is claimed that it does not have any significant toxicity in terms of passive exposure. Passive exposure to e-cigarette was compared with passive exposure to cigarette and the concentrations in the air of closed environment were tested and investigated. When compared with the exposure to cigarette smoke, it was concluded that the concentration of e-cigarette smoke in the indoor environment would not have a harmful effect to human health (12). In addition, the level which will not constitute a health risk for the users being exposed to e-cigarette involuntarily has also been determined. As a result of the studies conducted, the estimated exposure limit was found to be <1% TLV. The estimated exposure limit is <5% TLV for formaldehyde and acrolein, the chemicals that can result from the use of e-cigarettes (10).

The cytotoxic and mutagenic effects of e-cigarette use were studied with AMES and S9 metabolic activation test. For this purpose, 21 different e-cigarette liquids were investigated. When the cytotoxicity of e-cigarette (46.17% of PG, 44.92% of glycerol, 8.11% of water, 0.8% of nicotine, and <0.5% of flavor) and the cytotoxicity that can be caused by cigarette smoke were compared through MTT test (3-4,5-dimethyl-thiazolyl-2,5-diphenyltetrazolium bromide), the fibroblast viability was found to be lower in the cigarette extract. The liquid of e-cigarette was found to be less cytotoxic in comparison to the liquid of cigarette (13). The potential irritant effect that the e-cigarette aerosol can cause to the respiratory system needs to be investigated. For this purpose, the possible cytotoxic effect of e-cigarette aerosol was investigated by acute in vitro MTT cytotoxicity test in three-dimensional human respiratory tracts (3D The EpiAirway™). As a result, it had been found that cigarette smoke causes a dose-dependent decrease of up to 12% in cell viability, but no decrease in cell viability was observed when the cells that were exposed to e-cigarette vapor were compared to the results in the control group that was exposed to cigarette smoke and e-cigarette vapor. It has been concluded that e-cigarette has a lower cytotoxic effect in comparison to cigarette smoke (14).

Applications made to the toxic centers due to the use of e-cigarettes

Cervellin et al. (15) reported the poisoning due to the liquid content of e-cigarette for the first time. Poisoning occurred because of the ingestion and injection of the nicotine in e-liquid. A 22-year-old woman with chronic opioid dependence was admitted to the emergency service with complaints of tachycardia, redness in the body, and nausea. The patient had a bottled solution that was prepared by mixing e-cigarette liquid with methadone, and she consciously drank this mixture and injected 2 mL of this solution 2 h before coming to the emergency service. It was reported that the e-cigarette liquid that was used contained 18 mg/mL of nicotine. After the investigations and calculations, it was determined that the patient injected 2–3 mg of nicotine intravenously. The patient, in whom orogastric lavage and active charcoal were applied for treatment, was referred to the Addiction Service after psychiatric consultation. In a study examining the safety influences of e-cigarette usage on children, questionnaires on the healthcare and safety effects of e-cigarette usage were conducted for the parents who applied to the pediatric service (Washington University Pediatric and Adolescent Ambulatory Research Consortium) between June 24 and November 6, 2014. It was concluded that e-cigarette was used in one of every eight households that had a small child, and many parents were not informed about potential health and safety threats, including nicotine poisoning, that could be caused by e-cigarette. Of the people who participated in the study, 34.5% reported that e-cigarette would not adversely affect their child's health (16). In the United Kingdom, there are different case reports indicating that 18-month, 30-month, and 2-year-old children were

Table 4. PG toxicity (29)

Experimental animal species	Exposure	NOEL	Toxicity test	Day
Rat (Sprague Dawley)	Inhalation	20 mg/kg/day	Acute	28 days
Dog (Beagle dog)	Inhalation	6.05 mg/kg/day	Acute	28 days

PG: Propylene glycol

hospitalized because of nausea, lethargy, and ataxia after drinking e-cigarette liquid and were discharged 24 h later. In the case reports, no information was given about the amount of e-liquids that the children drank (17, 18). Studies on the acute effects of e-cigarette have shown that e-cigarette causes a gradual increase in the heartbeat and plasma nicotine levels within 5 min of the first intoxication (19). Studies have also shown that drinking an e-cigarette liquid or injecting it into the body can create new cases of acute poisoning.

There are also studies that indicate that e-cigarette may be risky for health (20). The conducted researches show that 82% of the users think that e-cigarette is not completely safe in terms of health, but they find it safer in comparison to smoking cigarette (21). The scientific literature, particularly the study (22) which shows that the amount of nicotine in e-cigarettes is 1.5 times more than that of classical cigarettes, emphasizes that e-cigarette toxicants should be evaluated in terms of harmful effects that they can cause to human health. The fact that e-cigarettes are sold both freely and via internet has increased the number of young people purchasing e-cigarettes (23). According to the results of the CDC (Centers for Disease Control and Prevention) analysis, e-cigarette use among adults in the United States has increased fourfold between the years 2009 and 2010 (24). While the use of cigarette decreased in the eleventh-grade students between the years 2011 and 2013, the use of e-cigarette increased from 2% to 5% in Oregon. Between the years 2011 and 2013, 31 calls were made to the Oregon Poison Center due to over-exposure or undesired exposure to nicotine in e-cigarettes (25). Between 2010 and 2014, 2,405 calls were made to the poison center in the United States due to e-cigarette and 16,248 calls due to smoking cigarettes. While the number of calls made to the poison center due to e-cigarette exposure was only one in February 2010, this number increased to 215 in September 2014 (26).

Chemical substances in e-liquid

Propylene glycol

Exposure to PG, which is mainly used to generate smoke and fumes, may occur dermally or through inhalation (27). The main component of the e-cigarette liquid is usually PG dissolved in water. When the user inhales from e-cigarette, this is detected by the mechanical sensor and the heater that is controlled by a microchip is triggered (28). PG is an alcohol derivative that is also called propane-1,2-diol/1,2-dihydroxypropane/methyl glycol. It is used as additives in foods and as a moisturizer and as an emulsifier in cosmetic products (E1520). Owing to this feature, it is also used in a similar way to prevent the drying of tobacco. It exists as a solvent in many pharmaceuticals (for those not soluble in water) such as benzodiazepines and phenytoin. It is also used by adding glycerin into PG at various concentrations. The reason for this is to prolong the life of aerosol in e-cigarette when in contact with air. PG is absorbed in the small intestine and is converted through glycolysis into components such as pyruvic acid or lactic acid, or through the ethanol pathway, it forms propionic aldehyde which is an acetic acid and a toxic substance. Non-metabolic PG is excreted directly in the urine or as a result of hepatic glucuronidation. The half-life of PG is 2 h in blood and 4 h in the body. According to the literature, PG has low toxicity in acute and chronic exposures. No toxic effects were observed in tissues, such as lungs, liver, and kidney, in the toxicity tests performed. When the toxicity of PG through inhalation was investigated, the NOEL (No Observed Effect Level) value was found to be approximately 20 mg/kg in small mammals. The data of PG toxicity are shown in Table 4 (29).

Long-term toxicity through inhalation or ingestion has not been observed in rats, and there is no evidence of a carcinogenic or genotoxic effect (10, 29–32). PG has an irritant effect on eyes. The time-weighted average (TWA; maximum 8 h) value for PG is 155 mg/m^3 (50 ppm, converter factor: 1 ppm=0.00311 mg/L) in total for smoke and aerosol and 10 mg/m^3 for only aerosol (27). PG can theoretically cause poisoning because it is a di-alcohol. Oxidation of PG at high temperature can produce toxic propionic aldehyde, lactic acid, pyruvic acid, and acetic acid. According to the safety data for European Chemical Marketing (REACH), PG does not have toxicity through inhalation but only has a slight irritant effect on the skin. There is no concentration limit that has been determined by the experts in the United States or France. However, the total limit value in the vapor was determined as 474 mg/m^3 in England. The toxic effect of PG on long-term exposure has been investigated on humans in places where smoke machines are used. According to the FDA, the fume that contains PG and is produced by the smoke machine has been classified as safe. However, no study has yet been conducted on the long-term toxic effects of PG when inhaled through e-cigarette (28).

Glycerol

Glycerol is used in some e-cigarette brands as a mixture instead of PG or along with PG in order to extend aerosol life. It forms toxic acrolein by evaporation at high temperature. Contrary to this, it is widely used in food and chemical industries and it is not toxic. Absorbed glycerol is metabolized in the liver and is converted into carbon dioxide and water or glucose and glycogen (28). The TLV of PG and glycerol is 10 mg/m^3 at the end of 8-h exposure (33). The volume of aerosol that is inhaled from e-cigarette is lower than the total volume of air, and according to the calculations, it is assumed that each breath taken contains an equal amount of aerosol (11). The rate of inhalable aerosol concentration for stage fumes which also contains PG is 0.70 mg/m^3 (34). The acceptable exposure limit was found to be 50 mg/m^3 (in case of an exposure of more than 8 h) in the studies conducted on PG and occupational exposure. When calculating these rates, it should be indicated whether the consumer uses e-cigarette liquid with low nicotine ratio or without nicotine. The upper limit of exposure to PG and glycerin is important for e-cigarette smokers because the likelihood of liquid consumption in larger volumes will increase in proportion to nicotine (10).

Food flavors

E-cigarette produces a white and odorless vapor with the mixture of PG or PG and glycerol in the liquid. For this reason, natural or artificial substances are added to give this mixture flavor. E-cigarettes contain flavored compounds such as menthol, vanilla, fruit, caramel, coffee. The nature of flavor enhancers has not been explicitly stated as in other herbal flavorings. But most probably, they are thought to belong to the group of food additives. No data are available on short- and long-term effects for the exposure to inhalation of food flavorings. However, some artificial sweeteners have been reported to be cytotoxic (35). Generally, the chemical composition of the e-cigarette liquid is not given by the manufacturers. The chemical content is not completely available on an e-cigarette package. For example, the chemical composition of e-cigarette liquid is given as 75.5% of glycerol, 24.5% of additive substance, and 8% of artificial flavor (28).

Nicotine

The oral LD50 value (lethal dose 50%) of nicotine is 50 mg/kg for rats, 3 mg/kg for mice, and between 0.5 and 1.0 mg/kg for adult humans. Because of the low LD50 level, nicotine is a highly toxic compound. Cigarettes contain approximately 8–20 mg of nicotine, and about 1 mg of nicotine is absorbed in each cigarette (36, 37). Because of nicotine poisoning, abdominal pain, sweating, fatigue, confusion, seizures, and death due to muscle paralysis in the respiratory system can occur. While low-dose acute nicotine poisoning results in tachycardia and hypertension, bradycardia and hypotension occur with high doses (37). The concentration ratio of nicotine in the liquid content of e-cigarette varies between 6 and 36 mg/mL. The liquid in the cartridge is labeled as low, medium, and high according to the amount of nicotine in the content. Each cartridge in an e-cigarette is used for about 300 breaths. Results of the investigation of the e-cigarettes of the same brand containing low, medium, and high amounts of nicotine showed that while 10.6 µg of nicotine/100 mL is inhaled in each breath that is taken in the liquid containing mid-level of nicotine, 26.8 and 43.2 µg of of nicotine/100 mL is inhaled in each breath that is taken with the heating of the 100-ml liquid containing high level of nicotine. It was found to be 0.35 µg/100 mL in another brand of an apple-flavored e-cigarette containing zero nicotine. Studies to determine e-cigarette cotinine and nicotine levels have been performed on body fluids such as saliva, plasma, and urine (7, 38, 39). For example, while the serum cotinine levels were found to be 2.4±0.9 ng/mL in those passively exposed to e-cigarette smoke, this value was found as 2.9±0.6 ng/mL in those passively exposed to cigarette smoke (7). A 0.35 µg/100 mL nicotine intake was measured by heating 100 mL of liquid (38). E-cigarette users consume approximately 120–175 breaths/day of e-cigarette smoke on average (40). On the other hand, serum cotinine levels of e-cigarette smokers and individuals exposed to e-cigarette smoke were found to be very similar to smokers. In this study, depending on e-cigarette smoking and classical cigarette smoking, serum cotinine levels were found to be 60.6±34.3 and 61.3±36.6 ng/mL, respectively. Similarly, while serum cotinine levels have been found to be 2.4±0.9 ng/mL in those who are passively exposed to e-cigarette smoke, this value has been found as 2.9±0.6 ng/mL in those who are passively exposed to cigarette smoke (7). When the amount of nicotine, another substance in the e-cigarette ingredient, was investigated, it was found that about 50% of the nicotine in the cartridge evaporated after 150–180 breaths of smoking (41). Generally, the amount of nicotine in these products varies from 0 to 20 mg/mL depending on the brand (42). Nicotine levels in 16 different e-cigarette cartridges were measured, and the nicotine ratio was found to increase up to 85% in the cartridge where the nicotine level was ranging from 4 to 24 mg. While the findings indicated that the nicotine levels were 0.5 and 15.4 mg in the cartridges containing high amounts of nicotine at the 300th breath, this ratio was between 0.5 and 3.1 in the cartridges containing low-moderate nicotine. The results show that the rate of nicotine evaporation in different cartridges is different and therefore the amount of exposure may be different (41). The nicotine level was found to be 1.7 and 51.3 µg at a single breath. Repeated test results conducted on three different cartridges by the FDA indicated that the amount of nicotine was 26.8 to 43.2 µg at each 100 mL of smoking (43). In another study conducted, the ratio of nicotine taken from the cartridge at each 150th breath was found to be ranging from 5.0 to 5.3 mg (41), contrary to the FDA results. Although the studies conducted on the analysis of chemical substances resulting from e-cigarette smoking are new as mentioned, chemicals have been identified from its use. The short-term effects of e-cigarette that is one of the ENDSs have been studied, and as a result of pharmacokinetic analyses, it was determined that it changed the level of serum nicotine level to 1.3 ng/mL in the first 20 min of ingestion. However, the long-term effects are not currently available (44).

Chemical substances released by using e-cigarettes

Tobacco-specific nitrosamines

Tobacco-specific nitrosamines (TSNA) are a group of carcinogens found in only tobacco products. TSNAs are formed by tobacco alkaloids and nicotine nitration. TSNAs are not found on fresh green tobacco leaves. The nitrate found in tobacco leaves is reduced to nitrite and forms TSNAs, which are tobacco alkaloids. It is estimated that daily exposure to TSNAs is 20 mg for smokers and 68 mg for snuff users. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone) and its metabolites have also been identified in the urine of non-smokers due to the exposure to environmental tobacco smoke. In relation to smoking, TSNAs play an important role in cancers of the esophagus, pancreas, and oral cavity. NNK, NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), and NNN (*N*-nitrosonornicotine) are shown to be important in the induction of cancer. NNN and NNK have an important place in the induction of oral cancer. The transformation of TSNAs into a DNA adduct depends on their metabolic activation. There are seven known TSNAs (NNN, NNK, NNAL, *N*-nitrosoanatabine (NAT), *N*-nitrosoanabasine (NAB), iso-NNAL, and 4-(*N*-methylnitrosamino)-4-(3-pyridyl) butyric acid (iso-NNAC)), but the most important ones identified in experimental animals are NNK, NNAL, and NNN. NNK and its metabolite NNAL cause the increase of O_6-meG and other methylated bases. TSNAs lead to alkylation in DNA as a result of metabolic activation. However, NNN can lead to the formation of pyridyloxobutyl that is a DNA adduct at O_6-G and other positions. All nitrosamines were found in tobacco products, except for NNA (4-methylnitrosamino)-4-(3-pyridyl) butanal (45).

TSNAs, known to be carcinogenic, were found in half of the samples that were examined according to the research performed on 18 e-cigarette cartridges (5). It is seen that electronic cigarettes have a higher amount of NNN when compared with nicotine replacement products such as nicotine band and nicotine gum in terms of TSNAs, and NNK is higher in nicotine band than in e-cigarette. It is seen in Table 5 that TSNAs such as NNN, NNK, NAT, and NAB are quite low in e-cigarette when compared with cigarette (9, 46).

In a study conducted in the United States with 12 different e-cigarette samples, carbonic compounds and volatile organic compounds, especially acetaldehyde and TSNAs, were detected in e-cigarette smoke. Every 15 breaths taken from e-cigarette correspond to one cigarette, and 0.20–5.6 µg of formaldehyde, 0.11–1.136 µg of acetaldehyde, 0.07–4.19 µg of acrolein, and 0.02–0.63 µg of toluene is taken on average. In addition, *p*/*m*-xylene and nitrosamine compounds NNN and NNK that are among the most carcinogenic compounds for humans have been identified in e-cigarette smoke (6). As is known, TSNAs can cause cancer, and NNK that is one of *N*-nitroso compounds can increase the amount of 8-oxo deoxyguanosine in DNA by causing single-chain fractures (45).

PAHs

PAHs that are among the chemical substances of e-cigarette have been measured in aerosol and fluid in some studies (9, 46). In a study conducted by Laugesen (9), 34 PAHs were examined in the liquid in e-cigarette cartridge, and anthracene, phenanthrene, 1-methyl phenanthrene, and pyrene were found. The PAHs detected in e-cigarette contents are the PAHs in the group (IARC Group 3) that has not been classified as carcinogenic by IARC (the International Agency for Research on Cancer). In a different study, no PAH was found in most of the aerosols analyzed in e-cigarettes, except for chrysene (46).

Heavy metals

E-cigarette investigations have revealed both toxic metal and silicate particles in both the e-cigarette liquid and the aerosol. The aerosol contains >1 µm tin, silver, iron, nickel, aluminum, silicate particles, tin nanoparticles (<100 nm), chromium, and nickel particles. The concentration of these nine elements examined in the e-cigarette aerosol was found to be equal to or greater than the concentrations in the cigarette smoke. As a result, many chemicals that can cause respiratory system disorders and diseases have been detected in the e-cigarette aerosol (47). In another study, 12 metals that could be exposed because of electronic cigarette were investigated, and cadmium, lead, and nickel metals were found at different levels (6). Although the levels of these compounds are less than those of cigarette smoke, most of them are carcinogenic compounds. Heavy metals such as tin, aluminum, cadmium, lead, and selenite have a feature of potential endocrine disruptor and they are known as metalloestrogens. In addition, some substances may exhibit higher toxicity when they are in nanoparticle size. Contrary to old toxicological risk models, with the thought of "less is more," with the decrease in particle size, it is possible that the compound easily passes through the defense mechanism of the body and shows toxic effect (47).

Acrolein, diethylene glycol, and formaldehyde

The main principle in the use of e-cigarettes is that the power supply heats the e-liquid in the cartridge. It is stated by the e-cigarette producers that the temperature in the evaporation chamber is 40°C–65°C (43). However, there is no information about the temperature range of the evaporation chamber on the e-cigarettes that are used. The same lack of information also exists for the evaporation temperature of PG/glycerol or glycerol in the evaporation chamber; for example, glycerol evaporates at high temperature but no evidence about the effects of glycerol or PG at high temperatures has been demonstrated because it is not known to what level the temperature in the chamber of e-cigarette increases. Some manufacturers have indicated that the chamber temperature is kept below 100°C, thus the toxic acrolein degradation caused by the high temperature is avoided (28). However, some studies have reported that the temperature exceeds 350°C when the solution in the cartridge is heated by the battery (8, 48).

Table 5. Comparison of TSNA levels (9, 46)

Product	NNN	NNK	NAT	NAB	Total (ng/g)
Electronic cigarettes	3.87	1.46	2.16	0.69	8.18
Nicotine gum	2.00	ND	ND	ND	2.00
Nicotine band	ND	8,00	ND	ND	8.00
Cigarette	2,900	960	2,300	100	6,260

NAB: N-nitrosoanabasine; NAT: nitrosoanatabine; ND: Not determined; NNK: N-nitrosonornicotine ketone; NNN: *N*-nitrosonornicotine

Acrolein causes irritation in the nasal cavity and lungs, thus providing grounds for the development of heart-related diseases. Because the inhalation of e-cigarette smoke leads to the intake of these compounds found in the smoke, high levels of irritation can occur in the mouth and throat. In particular, acrolein, formaldehyde, and acetaldehyde are released depending on the pyrolysis of glycerol by being heated in the cartridge of e-cigarettes (6). In addition, these chemical substances that have been detected also eliminate the arguments that e-cigarette smoke does not have compounds other than nicotine.

Besides acrolein, it is another important situation that formaldehyde which is a toxic compound due to high temperatures can form in e-cigarettes that are especially used directly with dripping technique (48). Diethylene glycol that is a toxic chemical used as an anti-freeze was identified in an e-cigarette sample investigated in a research conducted by the FDA (5). While formaldehyde has been identified by the IARC as one of the most important carcinogenic chemical compounds for human health, the same institution has identified acetaldehyde as one of the possible compounds that cause cancer in humans (49).

Diacetyl

Today, there are nearly 7,000 flavoring substances sold and used in e-cigarettes. At the beginning of the year 2000, diacetyl was associated with a disease named "Popcorn Lung". The amount of diacetyl, 2,3-pentanedione, and acetone, which are the most commonly used flavoring substances, was tried to be determined in a study conducted by Allen et al (50) in 51 e-cigarette cartridges with fruit, sugar, and cocktail flavors that are sold in markets. While the diacetyl limit of quantification (LOQ) value was found to be 239 µg/e-cigarette, LOQ for 2,3-pentanedione and acetone were found as 64 and 529 µg/e-cigarette. Diacetyl is known to cause bronchiolitis obliterans and some other respiratory system diseases due to occupational exposure in users. In particular, it has been concluded that the necessary assessments and regulations have to be made urgently concerning the exposure to flavoring substances in e-cigarettes such as particularly diacetyl.

In addition to the chemicals such as nicotine, PG, and glycerol, PAHs that occur as a result of burning or the chemicals, such as metals, nitrosamines, food additives, can also be exposed due to e-cigarettes use. Table 6 presents the toxicological assessment of the e-cigarette contents (liquid and vapor in the cartridge) according to IARC (19).

Table 6. Toxicological assessment of the substances in e-cigarette (49)

Group 1	Group 2B	Group 3	Unclassified substances
NNN[a]	Acrylonitrile[a]	NAT[a]	Nicotine[a]
NNK[a]	Propylene oxide[a]	NAB[a]	PG[a]
Benzene[a]	Acetaldehyde[d]	Acrolein[b]	Diethylene glycol[a]
Ethanol[d]	Styrene[e]	Xylene[e]	Acetyl pyrazine[c]
Formaldehyde[e]	Nickel[f]	Anthracene[e]	4-Hydroxy-2,5-dimethyl3 (2H) furanone[c]
Iron[f]	Lead[f]	Phenanthrene[e]	Acetone[d]
Aluminum[f]		1-Methyl phenanthrene[e]	Cresol[e]
Cadmium[f]		Pyrene[e]	Diacetyl[f]
		Chromium[f]	Tin[f]
			Silver[f]

Group 1, carcinogenic in humans
Group 2A, possibly carcinogenic for humans
Group 2B, probably carcinogenic for humans
Group 3, not classified as carcinogenic in humans
[a]Cartridge liquid; [b]Steam and cartridge liquid; [c]Cartridge liquid (food additive); [d]Cartridge steam; [e]E-cigarette vapor; [f]E-cigarette vapor and e-liquid
NAB: *N*-nitrosoanabasine; NAT: nitrosoanatabine; NNK: N-nitrosonornicotine ketone; NNN: *N*-nitrosonornicotine; PG: propylene glycol

CONCLUSION

In this review, the chemical substances in the liquid and vapor of e-cigarette, the literature on the potential health risks of these chemicals, and the information on the applications given to the poison centers due to e-cigarette until today have been presented. Numerous studies are needed to evaluate the effects of toxicity data occurring due to the use of e-cigarettes and to evaluate especially the long-term effects on health. The future studies on the effects of cigarette smoking should also be designed and implemented for e-cigarette use. In scientific studies, the exposure levels to PAHs that may lead to cellular damage and are included in e-cigarette content and other toxic and carcinogenic substances such as nitrosamines, heavy metals, and DNA adducts should be determined. New studies on the effects in people using cigarette and e-cigarette at the same time and the effects on the possible effects of passive exposure to e-cigarette smoke should also be planned. The knowledge on the possible effects of using e-cigarettes will be clarified as the number of studies increases.

Peer-review: Externally peer-reviewed.

Conflict of Interest: No conflict of interest was declared by the author.

Financial Disclosure: The author declared that this study has received no financial support.

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