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INVITED REVIEW

Known and Unknown Toxic Substances in New-Generation Tobacco Products

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Main Points

- New-generation tobacco and nicotine products have additional toxic ingredients different from those of conventional cigarettes.
- Electronic devices in these products cause the release of unexpected heavy metals due to heating and thermal degradation.
- Legal and illegal substances are likely to be added during uncontrolled production.
- Exposure to all toxic substances increases the magnitude of danger for dual users, adolescents, and young people.

Abstract

In recent decades, new-generation tobacco and nicotine products (NGPs) have been marketed to replace conventional cigarettes because of their health risks all over the world, despite their earlier marketing and production. However, studies indicated that NGPs also have some akin harmful effects besides unknown and undetermined ones. Toxic substances coming from tobacco plants or the heating process make these products dangerous as well as hazardous agents.

In this study, toxic substances and ingredients involved in electronic cigarettes and heated and smokeless tobacco products were reviewed, and their prevalence, quantities, and toxic effects were evaluated. Nicotine, tobacco-specific nitrosamines, volatile organic compounds, and some previously identified heavy metals are the prominent toxic substances involved in both conventional and new-generation tobacco products. However, studies conducted on e-cigarettes and heated and smokeless products showed that propylene glycol, glycerol, flavoring agents, and unexpected substances such as illicit or licit drugs, rare metals, and heating-based toxic chemicals are only the tip of the iceberg. Although NPGs are intended to be consumed instead of conventional cigarettes, the number of dual users is substantial, and the long-term effects of these products have not been clarified yet.

Keywords: Aerosol, electronic liquid, heavy metals, humectants, nitrosamines, toxicity

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Introduction

Since the beginning of the 20th century, combustible cigarette use has increased despite all public health initiatives, and studies have shown that smoking has been a direct cause of cancer among many other diseases. Despite the harmful findings and cigarette sale bans, the tobacco industry has constantly found a way that promotes smoking, making it a normative behavior in societies (Boykan & Goniewicz, 2021). Based on the awareness that most of the proven harmful effects of cigarettes are caused by substances resulting from combustion products, the tobacco industry has turned this situation to their favor and launched new-generation tobacco and nicotine products (NGPs) claiming that these are a safer alternative to traditional cigarettes and can be useful for smoking cessation. In contrast to the fact that nicotine aerosolization devices have been developed by the tobacco industry since the 1960s, electronic cigarettes (ECs) only became commercially available and sold in the US and Europe in the

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2006 – 2007 periods (Boykan & Goniewicz, 2021; O'Brien et al., 2021). Countless types of NGPs have evolved since they were first introduced to the market, and in 2019 e-cigarette industry in the US was above $9 billion (Boykan & Goniewicz, 2021).

There are three main types of NGPs available on the market: (1) ECs (or electronic nicotine delivering systems- ENDS), (2) heated tobacco products (HTPs), and (3) smokeless tobacco products (snus and nicotine pouches). Although some literature evaluated non-nicotine e-cigarettes as a different subgroup, it could be evaluated under e-cigarettes, understanding some ECs contain nicotine and some can be nicotine-free, as the World Health Organization abbreviated electronic non-nicotine delivery systems (ENNDS).

ECs can be described as devices that heat a solution electronically, often containing nicotine, producing an aerosol known as "vapor." Vaping is the term used to describe the act of inhaling aerosols produced by ECs. The general construction of an EC has a battery, an atomizer, and a liquid reservoir, which is the same across all models. Since ECs are the first NGP, they have been launched under different generations, altering their contents, features, and appearances. First-generation ECs are known for their resemblance to conventional cigarettes and come with a fixed battery. Second-generation ECs are larger compared to first-generation ones and consist of rechargeable/refillable batteries and liquid cartridges instead of disposable ones. The "mods" or third-generation ECs provide extensive customizability, bearing no resemblance to conventional cigarettes or earlier generations in size. Fourth-generation products, on the other hand, called "pods" are quite small and tend to resemble everyday technological objects such as USBs to make them easily concealable. Batteries on ECs are key parts that help to modify the aerosol and nicotine delivery amount, creating a variability in nicotine uptake. In addition, nicotine is available in a protonated form in fourth-generation ECs, enabling higher concentrations than the free-base seen in earlier generations (Boykan & Goniewicz, 2021). Although ECs are frequently promoted as "reduced-risk" products and are advertised publicly as the harm reduction initiatives of cigarette firms, high concentrations of nicotine and the additional harms that may be caused by modifications in aerosol release suggest otherwise.

The second type of NGPs is HTPs. Thousands of chemical compounds produced when tobacco is burned are known to be the main causes of or potential risk factors for smoking-related illnesses. For more than 20 years, the idea of heating tobacco without combustion or smoke has been developed. The strategy behind these products is called "Heat-Not-Burn," i.e., tobacco is heated up to a temperature of 350°C rather than being burned. Due to the low likelihood of tobacco burning at those temperatures, fewer chemical toxicants are produced as compared to conventional combustible cigarettes (Başaran et al., 2019; Boykan & Goniewicz, 2021; Caponnetto et al., 2018). Unlike ECs, these products contain tobacco, which is their main difference.

The final product of NGP family is, so-called smokeless tobacco products, known as snus. It comes in the form of a pouch-packaged consisting of powdered tobacco and flavors. These products are marketed as a result of tobacco control policies and harm reduction studies, especially in some countries such as the USA and Sweden. Nicotine pouch, on the other hand, was released to the market as an advancement of snus nicotine products. Yet, a nicotine pouch does not contain tobacco, but it contains nicotine extract. Its usage is quite convenient by placing the product between the user's lip and gum and holding it there until the nicotine is released. No combustion occurs during usage; therefore, it is very discreet (Patwardhan & Fagerström, 2022; Tobacco Tactics & University of Bath, 2022). These products include moist snuffs, dissolvable tobacco products in the form of porous bags, strips, toothpicks, and mint. Although smokeless tobacco products are intended to serve as a way to quit smoking behavior, it is still not clear that the use of smokeless products reduces the harm of smoking cigarettes (K. Choi et al., 2012; Ramström & Foulds, 2006; Zhu et al., 2013).

Since the new generation products presented above have been on the market for a relatively shorter time than traditional cigarettes and are available in more varieties, the number of toxicologic, carcinogenic, and genotoxic studies, let alone long-term studies, is quite limited. The fact that they are marketed as innocent products and as less harmful alternatives to smoking or as a way to quit smoking also causes users to have a wrong perception. However, none of these products are as innocent as they are presented to be. Studies on content analyses of some of these products have argued that they may contain more toxic ingredients than previously thought and have the potential to contain many unknown chemicals that have not yet been revealed.

In this study, toxic substances and ingredients involved in electronic cigarettes, heated, and smokeless tobacco products were reviewed, and their prevalence, quantities, and toxic effects were evaluated.

Traditional Cigarettes Versus New-Generation Tobacco and Nicotine Products

Traditional tobacco smoke contains over 7000 chemicals, at least 250 of which are known to be harmful, approximately 70 of which can cause cancer and are referred to as carcinogens. Nicotine, carbon monoxide, hydrogen cyanide, benzene, formaldehyde, acetaldehyde, acrylamide, polycyclic aromatic hydrocarbons (PAHs), nitrosamines, arsenic, cadmium, and nickel are among the most known of these carcinogenic chemicals. The majority of these chemicals are derived from the burning tobacco leaves, rather than from additives found in cigarettes (Dusautoir et al., 2021; The American Cancer Society, 2020). Since most of the information on the hazards of traditional cigarettes so far has been based on the chemicals produced by the combustion of the content, it can be placed among the most obvious expectations that none of these toxic chemicals will be found in the new generation products launched as safer alternatives to traditional cigarettes. There are studies that show smokers who switch to ECs (over a 4-week period) maintain their cotinine levels and have substantial declines in their levels of carbon monoxide and two of the eight tested volatile compound metabolites. However, studies have shown that these products may contain similar or additional toxic chemicals to those found in traditional cigarettes.

Harmful Chemicals in New-Generation Tobacco and Nicotine Products

The liquids in ECs mostly contain nicotine, solvents, and additives such as flavorings and sweeteners depending on their types. The majority of the time, the liquids used in ECs include nicotine, at least one solvent—typically propylene glycol (PG) or glycerol, flavorings, and additives. As previously mentioned, liquid content affects the amount of nicotine intake and toxicants in the aerosol that is released from the device. As opposed to open systems, which allow a variety of liquids with a wide range of properties, prefilled ECs have standardized liquid characteristics, for instance, PG/glycerol ratio and nicotine content. Since complete regulation on the production and sale of liquids has not yet been put into place in many countries, there are numerous manufacturers and brands of ECs liquids, as well as labeling problems all over the world. HTPs, on the other hand, use glycerine-soaked disposable tobacco sticks that are heated using an electric blade. Manufacturers claim to have reduced the majority of the toxic components contained in regular tobacco smoke by heating the product to a lower temperature, which prevents combustion (Dusautoir et al., 2021). Since combustion does not occur completely and dissolvable tobacco is used through oral ingestion in snus products as well, there is a perception by users that fewer toxic chemicals are produced (Choi et al., 2012; Zhu et al., 2013).

Harmful chemicals contained in or created by these NGPs are mentioned below in detail by general chemical classifications.

Nicotine is among the most addictive chemicals akin to illicit drugs; the majority of individuals who use ECs do so for the need of nicotine, though some prefer nicotine-free products. The nicotine content of ECs varies and is difficult to estimate due to reasons such as diverse percentage or concentration or inconsistent labeling and alterations in the mechanical composition, which increases the concentration of nicotine delivered to the user (Dusautoir et al., 2021; Goniewicz et al., 2019). Studies have shown that as the technology of EC advances, the nicotine levels in products also increase. The first reason for making this possible is the changes in their technical infrastructure, while the other reason is the use of nicotine in the protonated state instead of the free-base state (Boykan & Goniewicz, 2021; Gholap et al., 2020; Goniewicz et al., 2019). Comprehensive prevalence data studies revealed parallel results with these increased nicotine amounts. The use of ECs by middle and high school students increased dramatically between 2017 and 2018, rising by 48% and 78%, respectively (Glasser et al., 2021). According to recent research, around 25% of American college students between the ages of 18 and 25 are either now using ECs or have tried them at least once (Jones et al., 2021). Although the prevalence of the ECs has been attributed to their overall appeal, flavors, and advertising, perhaps another possibility is that the high and easily palatable nicotine content of pod products contributes to their continued usage and promotes symptoms of dependence among regular users, particularly among those who may have never smoked traditional cigarettes.

As for HTPs, according to research by Farsalinos et al., when the puff time is short, the nicotine concentrations in a certain brand of tobacco sticks are greater than those in ECs and generally comparable to those in regular cigarettes (Farsalinos et al., 2018). Some research, however, discovered that compared to the reference cigarette (3R4F cigarette), HTP supplied almost 30% less nicotine to its aerosol (Dusautoir et al., 2021). Basaran et al. mentioned that in HTPs, the nicotine amount was 84% of that seen in a conventional cigarette (Başaran et al., 2019).

Propylene glycol and glycerol are the most commonly used delivery solvents involved in EC liquids. These solvents work as humectants and are commonly known as "vegetable glycerin." Humectants like PG and glycerol are frequently used to maintain the moisture of the filler, to facilitate and soften the usage. Several studies determined both PG and glycerol substances in all liquid samples examined at a wide concentration range, some of which were not labeled despite being present in the products. Apart from these two toxic substances, other solvents such as 1,3-butanediol, ethylene glycol, diethylene glycol, and 1,3-propanediol were encountered in ECs (Hahn et al., 2014; Hutzler et al., 2014; National Academies of Sciences, Engineering, 2018; Uryupin et al., 2013). The Food and Drug Administration (FDA) categorized PG and glycerol as generally recognized as safe (GRAS) in 1973. Under the circumstances of their intended usage as food additives, substances that are designated as GRAS are thought to be generally safe. In this situation, it has been assumed safe for oral consumption but may not always be for other routes of administration, such as inhalation. However, the act of vaping heats and vaporizes these substances, and there is insufficient evidence to support the safety of food-grade substances for vaping (National Academies of Sciences, Engineering, 2018). According to a study, when PG and glycerol are heated in ECs, formaldehyde can be produced, which is a Group 1 carcinogen according to the International Agency for Research in Cancer (IARC) (Jensen et al., 2015). Although these chemicals are regularly used solvents not only for the liquid of ECs, but also for cosmetics, food products, plastics, and paint industries, therapeutic preparations and are assumed safe in oral route (Zar et al., 2007), there are several identified toxic effects resulting in allergic reactions, upper respiratory irritation, asthma, exogenous lipoid pneumonia, and even toxidrome (Choi et al., 2010; Werley et al., 2011; Wieslander et al., 2001). Given that HTPs use disposable tobacco sticks soaked in glycerol, Li et al. found higher amounts of glycerol in a commonly used brand of HTPs than 3R4F reference cigarettes (Li et al., 2019).

Carbonyl compounds, of which the most known and commonly encountered in tobacco products are formaldehyde, acrolein, and acetaldehyde, are classified as human carcinogens due to their adverse effects on the lungs (Dusautoir et al., 2021). There are a couple of explanations for how carbonyl compounds generate in NGPs such as the impurities previously involved in the e-liquids that are transferred into the aerosol; metals discharged by some device components; and heating the liquid in the device can cause the formation of carbonyls (Belushkin et al., 2020). Another claim is that sucrose (used as a sweetener) is most likely the primary source of carbonyls (Kubica et al., 2014).

The lack of standardization in the EC aerosol generation processes makes it challenging to compare results from the literature. Regarding the production of carbonyls in EC aerosol, there is, nevertheless, some agreement: glycerol and PG thermally decompose to create acetaldehyde, acrolein, and formaldehyde compounds. These substances have been found in EC aerosols at a variety of concentrations, ranging from below the quantitation limit to concentrations higher than those seen in conventional cigarette smoke (Kosmider et al., 2014). Studies on carbonyls in EC vapor revealed that 8 out of the 13 ECs contained formaldehyde or acetaldehyde. The quantities were lower in low-voltage EC vapors than in tobacco smoke, while the levels of high-voltage EC vapors were comparable to those of tobacco smoke (Kosmider et al., 2014). In another study, the aerosol of disposable EC devices had carbonyl contents that were lower compared to conventional cigarettes. This could be the result of the very low temperatures and power consumption that these products produce. Furthermore, according to a study, depending on the puffing regimen, formaldehyde concentrations may range from 20 to 255 ng/puff (Beauval et al., 2019). However, all the results of formaldehyde, independent of puffing regimen were below conventional cigarettes. In another study conducted with various types and brand ECs, all values were below the Association Française de Normalization (AFNOR) experimental voluntary standard for acetaldehyde, while 10 products were above for formaldehyde. The device-to-device variation was found to be over a wide range (20 – 100%; 1 – 120%) for the carbonyl groups analyzed, depending the system is opened or closed (Belushkin et al., 2020).

In contrast to the fact that the thermal breakdown of the PG and glycerol in the e-liquid is the primary source of formaldehyde and acetaldehyde formation, in HTPs, the thermal degradation and pyrolysis of tobacco are the source of known carbonyls (Auer et al., 2017; Dusautoir et al., 2021). Many carbonyls were detected in commonly preferred brands of HTP such as acetaldehyde, acetone, acrolein, formaldehyde, and butyraldehyde. Among these, none of them were comparable with the conventional 3R4F cigarette (Schaller et al., 2016). Similar results were obtained in another study that investigated the 3R4F under two different regimes. Reduction rates (difference between 3R4F and HTP product) ranged between 55 – 93% for the ISO regime and 68 – 96% for the HCl regime (Li et al., 2019).

Volatile organic compounds (VOCs) are organic chemicals that are present in a variety of items, including tobacco smoke, fragrances, paint removers, clothes, and plastics, and are easily absorbed into the environment. Volatile organic compounds and some other non-nicotine toxicants are more strongly linked to smoking-related morbidity and death than nicotine, despite nicotine's widespread perception as the major toxic ingredient (Haussmann, 2012). In a study that investigated 12 models of ECs, toluene, and m,p-xylene were found in varying amounts (Goniewicz et al., 2014). A study conducted in 2018 investigated the toxic VOCs released from ECs on young vape users (Rubinstein et al., 2018). Results revealed that higher concentrations of propylene oxide (2-hydroxypropylmercapturic acid), acrylonitrile (2-cyanoethylmercapturic acid [CNEMA]), acrylamide (2-ca rbamoylethylmercapturic acid [AAMA]), acrolein, and crotonaldehyde (3-hydroxy-1-methyl-propylmercapturic acid) chemicals were found in the urine of EC-only users compared to non-users. Comparing dual users to EC-only users and controls, there was a significant difference in the concentration of metabolites of benzene (phenylmercapturic acid [PMA]), ethylene oxide (2-hydroxy ethylmercapturic acid), CNEMA, 3-HPMA, and AAMA excreted in urine (Rubinstein et al., 2018). Another study conducted in 2020 discovered that methylmercapturic acid (MMA-the metabolite of methylating agents) concentrations of VOC metabolites in the scope were much greater during EC use compared to conventional cigarette use (Helen et al., 2020). When compared to abstinence, the within-subject concentrations of benzene and acrylamide (AAMA) metabolites were considerably greater after e-cigarette use. This study also discovered that the levels of the propylene oxide metabolite (2-HPMA) and 1,3-butadiene metabolite (MHBMA-3) varied substantially across EC devices, with variable-power tank users exhibiting greater amounts (Helen et al., 2020). This suggests that all the experimental results in the literature regarding ECs should be evaluated depending on the device and its properties.

As for VOC investigations in HTPs, isoprene, benzene, and toluene were found at lower concentrations than conventional cigarettes (3R4F), but they can still be found in trace levels (Li et al., 2019). Other studies also revealed that determined levels of benzene, acrylonitrile, 1,3-butadiene, isoprene, toluene, and pyridine found in the HTP products were much lower than those of conventional cigarettes (Schaller et al., 2016).

Tobacco-specific nitrosamines (TSNAs) are potent carcinogens that may easily enter the respiratory system by aerosol. Even though the manufacturer asserts that the device contains trace amounts of TSNAs, early research measured ten times the maximum amounts of total TSNAs in EC replacement liquids compared to the EC company's published values (Kim & Shin, 2013). Nitrosonornicotine (NNN), nitrosoanabasine (NAB), 4-(me thylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), and nitrosoanatabine (NAT) are the primary TSNAs found in conventional tobacco (Kim & Shin, 2013). Research revealed that two nitrosamines, NNK and NNN, were present in ECs; the amounts ranged from 0.8 ng to 4.3 ng and 1.1 ng to 28.3 ng, respectively, per EC (Goniewicz et al., 2014). In another study, a total of 105 samples from 11 different brands of EC liquids were examined to determine the TSNA levels present. The concentrations of TSNAs were measured to be in a range of 0.34 – 60.8 g/L for NNN, 0.09 – 62.19 g/L for NAT, 0.11 – 11.11 g/L for NAB, and 0.22 – 9.84 g/L for NNK. According to analytical results on the topic, the amount that ECs contain of TSNAs is very low as compared to conventional cigarettes, yet these carcinogenic substances can still be found in ECs (Goniewicz et al., 2014).

Schaller et al. conducted a research on aerosol of HTPs, findings notifying that all TSNA in the scope (NAT, NNK, NNN, and NAB) were detected, revealing lack of combustion in products does not prevent TSNA from occurring. Yet, the levels of the 4 TSNA substances detected were found approximately 90% lower than in conventional cigarettes (Schaller et al., 2016). A study by Li et al. in 2019 also showed that the amounts of NAB, NAT, NNK, and NNN detected in HTPs were 72 – 96% lower compared to conventional cigarettes, similar to the other studies in this field (Li et al., 2019).

As for snug products, after the preparation processes such as curing, cutting, drying, and grounding, smokeless tobacco products are treated with some chemicals and heating steps to prevent microbial degradation, long shelf life, and to obtain optimum moistening conditions. Studies showed that both moist snuffs and snus involve TSNA (NNN and NNK) in varying ranges (Rutqvist et al., 2011). Additionally, NNK and NNN were detected in some marketed products up to 7870 and 3805 μg/g, respectively, in dry weight (Idris et al., 1991). However, with the increasing awareness of this issue, it is suggested that a lot of work has been done and implemented to minimize and/or prevent TSNAs that occur in products during the production process or during the waiting period (Rutqvist et al., 2011).

Flavoring agents in e-liquids such as vanilla, chocolate, cinnamon, menthol, cotton candy, and fruit are among the most common reasons why EC is preferred. Similar to PG and glycerol, a number of flavors are considered GRAS for ingesting but not inhalation. Some flavors are known to be harmful, but much remains to be unknown about the health implications of flavor inhalation (Boykan & Goniewicz, 2021). When EC aerosols are inhaled, flavoring compounds are absorbed into the body, influencing the respiratory and oral systems (Gerloff et al., 2017). Diacetyl, 2,3-pentanedione, and 2,3-hexanedione are the most well-known toxic flavors. According to a recent research, diacetyl, pentanedione, and several other flavoring chemicals—such as acetoin (butter), diacetyl, maltol (malt), and ortho-vanillin (vanilla)—found in EC have been linked to serious health problems such as pulmonary fibroblasts and pro-inflammatory responses (Gerloff et al., 2017). A study showed aldehydes from 5570 to 7210 μg/g formaldehyde, from 2670 to 3640 μg/g acetaldehyde, from 172 to 347 μg/g acrolein, from 320 to 518 μg/g propionaldehyde can be detected in flavored e-liquids (Khlystov & Samburova, 2016). Some studies have also shown that flavoring agents increase or affect VOC production. For example, the CNEMA levels of participants who reported consuming fruit tastes over the last month were greater than those who did not (Rubinstein et al., 2018). In addition, sweetener additives such as sucralose have been added to EC liquids. Nevertheless, it was discovered that when sweeteners are heated, they may create furans and aldehydes. Information about the toxicity and short- and long-term health impacts of inhaling flavoring compounds is lacking. Tobacco producers have recognized that young people are drawn to flavored tobacco products; therefore, they will keep producing new ones until solid regulations pass.

Heated tobacco products are also marketed with added flavors, but these are not as diverse as in EC liquids. Generally, known flavors such as menthol are preferred because of their similarity to conventional cigarettes. Furans and pyridines found in HTPs are produced when flavors are heated. These chemicals are typically found in relatively high amounts compared to other combustion materials (Bekki et al., 2021) and research has shown that certain flavoring compounds may cause bronchiolitis and obstructive lung disorders. A comprehensive study revealed that menthol, limonene, and vanillin were found in many products in the scope, as well as PG and glycerol, which were serving as transporters for flavors. It appears that the overall amount of flavor utilized in HTPs is around twice that of regular tobacco consumption (Lim et al., 2022).

Toxic metals are inevitable consequences of NGPs since both ECs and HTPs are based on the device principle. Among the NGPs, ECs contain more metal components than other products depending on their formation and modifications. E-liquids and EC aerosols are composed of inorganic elements and therefore raise further concerns about their safety. Inorganic elements commonly found are nickel, lead, chromium, copper, zinc, and silver. It is a known fact that some metals detected in EC aerosols and liquids, especially nickel and lead, have carcinogenic effects in the case of chronic exposure. Inhalation of metals from EC use may cause adverse health effects such as coughing, wheezing, chest tightness, breathlessness, and a metallic taste in the mouth (Mercan, 2020; Williams et al., 2017). In one of the prominent studies conducted by Williams et al. with 13 electronic tobacco products (in the aerosol) including both ECs and electronic hookahs, out of the investigated 36 inorganic elements, 35 were detected, while only 15 of these 35 elements were found in conventional cigarettes. The remaining elements were considered as only coming from electronic parts of products such as the filament for nickel and chromium, thick wire for copper, brass clamp for copper and zinc, joints for tin and lead, wick and sheath for silicon, calcium, magnesium, and aluminum. Additional results showed significantly higher concentrations of copper, lead, nickel, and tin in EC aerosols than in combustible tobacco smoke (Williams et al., 2017). Tobacco grown on soil is subject to air, water, and soil pollution in the growing region, which could be another potential source of heavy metals. Tobacco in the NGPs can be seriously affected by these pollution sources (National Academies of Sciences, Engineering, 2018; Williams et al., 2017). Moreover, cadmium, lead, arsenic, nickel, and chromium were identified and maximum permissible limits were regulated with Gothiatek standard (www.gothiatek.com) in snug products as well (Rutqvist et al., 2011).

Other chemicals were also studied besides already known parameters such as the level of nicotine, formaldehyde, flowering substances, humectants, and so on. However, considering how much even the concentrations of known substances vary according to product type, content, and characteristics, the number of unknown substances that have not yet been analyzed in NGPs may be higher than is thought.

As one of the most dangerous groups of chemicals, PAHs can be determined in NGPs as well as in conventional tobacco cigarettes. They are formed by incomplete combustion or pyrolysis of organic materials such as coal and/or tobacco leaves. In this substance family, benzo(a)pyrene (BaP) is determined as a Group 1 carcinogenic substance according to IARC. It's also known that smoking conventional tobacco products and hookahs also generates BaP. Studies identified this toxic agent in NPGs as well. A study demonstrated that investigated HTP produced more PAHs than the three ECs in the study. To illustrate, BaP concentration was approximately 23 pg/puff, while three ECs were up to 6.1 pg/puff. However, the PAHs resulted in the HTP were far below conventional tobacco cigarettes, except benzo(c)phenanthrene, which in comparison to all other aerosols, was observed to have greater HTP emissions (Dusautoir et al., 2021). On the other hand, some studies showed PAH compounds were not found in the smoke of a certain brand of HTP (Başaran et al., 2019), suggesting that differences such as brand, model, modification, and flavor can lead to different products and concentrations even between models of the same brand. Moreover, undesirable substances such as BaP, nitrate, and N-nitrosodimethylamine (NDMA) were also seen in some products (Rutqvist et al., 2011).

As mentioned above, the presence of flavoring agents in HTPs may lead to the generation of furans and pyridines in the smoke of HTPs. Furans, which are generated also in food by the thermal breakdown of sugar, are among the detected chemicals, including 2-furanmethanol and 2(5H)-furanone. Pyridines (4-ethenylpyridine), which are created when nicotine is thermally broken down, were also found in HTPs' smoke (Bekki et al., 2021; St. Helen et al., 2018). These furans and many other toxic chemicals can be found in much higher amounts in a certain type of HTP than in conventional cigarettes, revealing that not all HTPs are innocent as claimed by the manufacturers (St. Helen et al., 2018).

Another danger is the unexpected pharmaceuticals and illicit drugs such as Δ9- tetrahydrocannabinol arising from these uncontrolled NGPs (Boykan & Goniewicz, 2021). Occasionally found ingredients in e-liquids include rimonabant, a medication for weight loss, and tadalafil, a medication for erectile dysfunction (Hadwiger et al., 2010). Concerns have also been expressed over the possibility of organophosphate flame retardants, phthalates, and pesticides that have not had their respiratory safety regularly assessed contaminating e-liquids and tobacco leaves (Wei et al., 2020).

The most broad-spectrum assessment emerged from the literature review is that NGPs are not as harmless as claimed. Although the determined levels of several toxic substances in these products are found relatively lower than in conventional cigarettes (i.e., nitrosamines), both organic and inorganic ingredients have well-known toxic effects such as carcinogenic, teratogenic, and/or DNA damage. Although the literature results are in favor of harm reduction or cessation, some toxicant exposure levels remain clinically concerning, especially for dual users. Also, harm reduction should not be misinterpreted as using NGP being harmless. Because, in particular, compared to older devices, the most recent generation of EC and HTP devices delivers larger quantities of nicotine and some other toxicants. It should also be kept in mind that adolescents and children are likely to suffer the most from the perception that e-cigarettes are harmless. This is because these products have been shown to pose many hazards that may adversely affect the development of children and adolescents and cause physiological and neurodevelopmental disorders. In many countries around the world, legal measures have been taken regarding the sale and use of these products, and in Türkiye, the sale, production, and import of NGPs have been banned since 2020. Despite these legal measures, it is observed that electronic tobacco products have lowered the age of tobacco use and have become increasingly dangerous, especially among children and adolescents. While the short- and long-term effects of these products, which contain many known and unknown toxic substances, are still unclear, it is considered essential that urgent action plans should be put in place for the best interest of future generations.

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