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Review / Derleme

Evaluation of scientific studies on electronic cigarettes in the last five years

E-sigara üzerine yapılan bilimsel makalelerin son 5 yıllık değerlendirilmesi

Nurhan Meydan Acımış[1], Simge Peşdere[1]

[1]Department of Public Health, Faculty of Medicine, Pamukkale University, Denizli, Türkiye

ABSTRACT

Electronic cigarettes are not as harmless as claimed and contain substances known to be hazardous to human health. E-cigarettes include chemicals similar to those found in conventional cigarettes, such as formaldehyde, acetaldehyde, acrolein, diethylene glycol, nickel, chromium, and lead. In recent years, their use has become increasingly widespread in Türkiye, as in many other countries. The characteristics of these devices, their effects on human health, and their potential role in smoking cessation have attracted global attention. In this context, general information about e-cigarette devices and their usage, as well as studies conducted on these devices, have been reviewed. The studies in this area include surveys, clinical observational studies, and both clinical and interventional research investigating potential harmful effects. Currently, there is insufficient scientific evidence regarding the safety of e-cigarettes. Although it is often claimed that these products do not contain tobacco, they do contain nicotine, which is known to cause addiction. The aim of this review article is to highlight the characteristics of electronic cigarettes, their impact on human health, their global use, and to provide an objective perspective by examining the existing literature on the subject.

Keywords: electronic cigarette, tobacco, human health, smoking, tobacco cigarette

ÖZ

Elektronik sigara; söylenildiği gibi zararsız olmayıp insan sağlığı açısından tehlikeli olduğu bilinen maddeler ihtiva etmektedir. E-sigaralarda, sigaralardakinin benzeri (formaldehit, asetaldehit, akrolein, dietilene glikol, nikel, kromium, kurşun vb.) kimyasallar bulunmaktadır. Son birkaç sene içinde, diğer ülkelerde olduğu gibi, Türkiye'de de kullanımı bir hayli yaygınlaşmıştır. Bu aletin özellikleri, insan sağlığı üzerine etkileri, tütün sigarasını bırakmaya yönelik potansiyeli dünya çapında ilgi çekmektedir. Bu amaca yönelik olarak e-sigara cihazı ve kullanımına ait genel bilgiler ile cihaz üzerine yapılan çalışmalar incelenmiştir. Bu konuda yapılan

✉ Nurhan Meydan Acımış ▪ nurhan88@hotmail.com

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çalışmalar; anketler, klinik gözlem çalışmaları ile potansiyel zararlı etkilere yönelik klinik ve girişimsel çalışmalar şeklinde detaylı bir şekilde gözden geçirilmiştir. Günümüzde e-sigaraların güvenilirliğine ilişkin yeterli bilimsel çalışma yoktur. Her ne kadar bu sigaraların tütün içermediği iddia edilse de içlerinde bağımlılığa yol açan nikotin bulunmaktadır.

Bu derleme makalenin amacı; Elektronik sigaranın özellikleri, insan sağlığı üzerine etkileri, dünya çapında kullanımına dikkat çekmekte ve konu üzerine yapılan yayınları gözden geçirerek okuyucuların objektif bir bakış açısına sahip olmalarının sağlanmaktır.

Anahtar kelimeler: elektronik sigara, tütün, insan sağlığı ve sigara, tütün sigarası

Introduction

General information about e-cigarette devices and their use

Definition of e-cigarettes

E-cigarettes are handheld, battery-powered devices that simulate the structural, behavioral, and physiological aspects of conventional cigarette smoking.[1] These devices typically consist of a battery, a liquid-containing cartridge, and a heating element housed within a vaporization chamber.[2] The liquid, often referred to as e-liquid or vape juice, contains a solvent mixture of propylene glycol, glycerin, flavorings, and nicotine. When heated, this liquid produces an aerosol that is inhaled into the lungs.[3] The aerosol rapidly passes through the heart and delivers nicotine to the brain within seconds. It has been reported that electronic cigarettes are approximately 95% less harmful than conventional tobacco cigarettes.[4] Smokers have claimed that switching to e-cigarettes can aid in quitting traditional smoking, and some studies have found them to be more effective than nicotine replacement therapy.[5]

Historical background of electronic cigarettes

The concept of electronic cigarettes (e-cigarettes) first emerged with Herbert A. Gilbert's 1963 patent for a "smokeless, non-tobacco cigarette."[6] However, the modern form of the e-cigarette was developed in 2003 by Chinese pharmacist Hon Lik through a patented design by the Ruyan company.[7] E-cigarettes have since evolved from first-generation models that mimic traditional tobacco products to newer generations resembling everyday objects such as USB flash drives.[7-9] Their basic components include nicotine or non-nicotine liquid cartridges, an atomizer, and a lithium battery, while additional features such as flavorings and LED lights have been introduced to enhance user experience.[7,10,11]

Market data indicate that between 2010 and 2012, sales increased from 750,000 to 3.5 million units.[12] In Türkiye, 91% of 96 active e-cigarette sales websites do not display any age restriction warnings, and 56% claim that e-cigarettes assist in smoking cessation.[13] It has been found that 97% of users are former cigarette smokers, most of whom turned to e-cigarettes under the perception that they are "less harmful."[14] However, scientific studies report conflicting results: while research supported by Ruyan emphasizes low nicotine absorption and the absence of carbon monoxide, FDA analyses highlight the presence of carcinogenic chemicals.[15] Marketing strategies often focus on terms such as "harmless," "economical," and "socially acceptable."[16]

Prevalence of e-cigarette use among adolescents

The increasing prevalence of electronic cigarette use among adolescents is associated with the novelty of the device, the perception that it is less harmful than traditional cigarettes, and the wide variety of available flavors. Nicotine has particularly

detrimental effects on brain development in adolescents, who are more vulnerable to its addictive properties. While e-cigarette use is more common among unemployed individuals, manual laborers, and males, it is often preferred by adults as a smoking cessation aid, and by women and pregnant individuals due to the belief that it poses fewer health risks.

However, e-cigarettes may contain heavy metals such as nickel, chromium, and cadmium, which can have harmful effects on health. E-cigarette use has been associated with exacerbation of diseases such as chronic obstructive pulmonary disease (COPD). Although some symptoms may reverse after cessation, certain types of tissue damage may be permanent. While most cases of acute lung injury related to e-cigarette use are treatable, deaths have also been reported.

Effects of e-cigarettes on organ systems

Aerosols cause inflammation of the lingual frenulum, thereby damaging oral health.[17] The most common gastrointestinal symptoms reported are epigastric pain, nausea, and vomiting, followed by diarrhea and bleeding.[18] An increase in heart rate and blood pressure has also been documented.[19] Improvements in time-dependent memory and nicotine withdrawal symptoms have been observed following cessation of conventional smoking and transition to e-cigarettes.[19] In particular, chronic nicotine exposure during adolescence has been shown to result in long-term adverse effects on memory and attention.

It has been reported that toxic and carcinogenic substances are present at lower levels in e-cigarettes compared to conventional cigarettes; however, some users have been found to have unexpectedly high levels of carcinogens.[20] Cadmium content in e-cigarettes contributes to DNA damage along with its potential carcinogenic effects.[21]

Effects on health and public health

In 2019, an outbreak of lung illness associated with electronic cigarette use was reported in the United States, affecting 2,807 individuals and resulting in 68 deaths. This condition, presenting with symptoms such as shortness of breath, cough, chest pain, hemoptysis, fever, and fatigue, was linked to Vitamin E acetate and THC found in e-cigarette liquids.[22] The CDC emphasized that children, adolescents, and young adults are particularly at risk, urging families and educators to exercise caution.[23] A systematic review examining 76 studies concluded that e-cigarettes are harmful to health and increase the risk of bronchitis and myocardial infarction. Conversely, some studies indicate limited short-term effects and insufficient evidence regarding long-term outcomes.[24] Another review analyzing 26 case reports showed that e-cigarette use can lead to pneumonia, bronchiolitis, ulcerative colitis relapse, infections, and cardiac and neurological complications.[25]

E-cigarettes may contain carcinogenic chemicals and can cause physical injuries due to battery explosions.[26] They have been reported to increase the risk of cardiovascular and respiratory diseases, as well as cause fetal effects.[27] The CDC states that while e-cigarettes may be less harmful than traditional cigarettes, this does not imply they are “safe.” The risks vary among individuals and not all e-cigarette products are identical.[27] A meta-analysis of 38 studies found that e-cigarette use reduced smoking cessation rates, whereas another review of 62 studies reported a positive association with quitting smoking but noted methodological weaknesses in the studies.[28,29] A randomized controlled trial (RCT) demonstrated that e-cigarettes have similar effectiveness to nicotine gum.[30]

A review of 16 studies reported that passive exposure to e-cigarette vapor poses health

risks, although these are lower compared to conventional cigarette smoke.[31] As of 2020, the United States had reported a total of 2,807 cases and 68 deaths, with a median patient age of 49.5 years.[32] Clinical findings prominently include shortness of breath, chest pain, cough, fever, and hypoxia.[18] A detailed history including e-cigarette use within the past 90 days is critical for diagnosis.[33] Imaging often reveals bilateral ground-glass opacities predominantly in the lower lobes.[34] Radiological patterns may include acute eosinophilic pneumonia, diffuse alveolar damage, organizing pneumonia, and lipoid pneumonia.[35] Additionally, pleural effusion, pneumothorax, and pneumomediastinum may be observed.[18] Biopsy findings are nonspecific, showing inflammation, macrophage infiltration, and alveolar damage.[36] Systemic steroids are used in treatment, though further research is needed to determine optimal dosing and duration.[37]

According to the updated Tobacco Products Directive, manufacturers and importers are required to notify national authorities about the products they intend to market. The nicotine concentration in products is limited to a maximum of 20 mg/ml.[38] Although advertising, sponsorship, and annual reporting obligations exist, e-cigarettes are regulated under a relatively softer legal framework compared to conventional cigarettes.[39] The FDA mandates registration of sales points, labeling, content information, and health documentation, along with mandatory legal warnings on packaging.[40] The legal status of nicotine-containing and nicotine-free e-cigarettes varies by country.[41]

An in vitro study conducted in 2014 demonstrated that e-cigarettes affect the expression of cancer-related genes in lung epithelium.[42] A 2015 animal study reported increased oxidative stress and alveolar macrophage levels in mice exposed to e-cigarette smoke for two weeks, along with decreased immunity to bacterial (Streptococcus pneumoniae) and viral (Influenza A) infections.[43] Another study observed decreased glutathione levels and increased inflammatory cytokines in mice exposed to e-cigarette aerosols. Similarly, mice exposed to aerosol for four weeks showed increased inflammatory markers in bronchoalveolar lavage fluid, enhanced biofilm formation, and antibiotic resistance against Staphylococcus aureus infection.[44]

Intratracheal administration of nicotine-containing liquid increased Th2 cytokines and IgE levels, leading to respiratory tract inflammation.[45] Another study found that increased oxidative stress induced apoptosis in lung cells.[46] Neonatal mice exposed to nicotine aerosol exhibited lower body weights and signs of respiratory failure.[47] E-cigarette users have higher rates of anxiety and depression.[48] Nicotine and other agents increase IL-6 secretion, weakening the immune system and potentially contributing to respiratory diseases such as asthma and COPD.[49] Additionally, e-cigarettes increase the pathogenicity of Candida albicans by upregulating SAP gene expression and enhancing adhesion to the gingival epithelium, thereby raising the risk of oral candidiasis.[50]

The Growing Threat of E-Cigarettes: Electronic cigarette use is primarily intended as a means to quit traditional smoking; however, non-smokers also engage in e-cigarette use.[51] E-cigarettes operate through a mechanism that vaporizes a liquid contained in a cartridge, which is roughly the size of a conventional cigarette and refillable. This cartridge primarily contains propylene glycol and/or glycerol. Nicotine, various flavorings, and other substances can be added to the vaporized liquid.[52]

Preferences for e-cigarette use include its similarity in design and usage to traditional cigarettes and the perception that it is healthier than smoking.[43] Chronic bronchitis and asthma have been observed among young users of e-cigarettes, while a decline in lung function is

noted in older age groups.[53] Propylene glycol, upon heating and vaporization, converts to glycidol, which is a carcinogen.[54] Evidence exists indicating that e-cigarette vapor has carcinogenic potential and can activate cancer-related genes.[54]

Electronic cigarettes can also be used for the consumption of tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. Vitamin E acetate, used as a diluent for THC, has been identified as the primary causative agent of lung injury in e-cigarette users. Other e-cigarette products and additives also have the potential to cause acute lung damage.[55]

In Türkiye, electronic cigarettes are classified as "tobacco products" under Law No. 4207 on the Prevention and Control of Tobacco Products Harm. No licenses have been issued for e-cigarettes in Türkiye, and existing products enter the market through illegal means.

Current status of e-cigarette use globally and in our country

Tobacco remains one of the leading causes of preventable death worldwide, with approximately 1.2 billion people using tobacco products and 7.1 million deaths attributed to tobacco-related causes annually.[56] In Türkiye, about 16 million people use tobacco, resulting in approximately 100,000 deaths each year.[57] The FDA's classification of e-cigarettes as nicotine-containing products and the mandatory warning label stating, "This product contains nicotine. Nicotine is an addictive chemical," have influenced regulatory approaches toward e-cigarettes.[58] Although some e-cigarettes are marketed as "0% nicotine," analyses have detected the presence of nicotine in these products.[59]

Among the population, 39.8% of women and 57.77% of men are active smokers. Smoking behavior has been found to be associated with marital status, with married individuals demonstrating higher cessation attempts, and usage rates decreasing as educational level increases. However, no significant relationship has been observed between educational level and e-cigarette experience. Approximately 40.6% of participants indicated that they prefer e-cigarettes for "health" reasons, 44.4% for "hygiene," and 40.8% for "economic" considerations. E-cigarettes may pose a risk of new nicotine addiction, especially among youth who have never smoked. In a follow-up study, 81% of new e-cigarette users continued usage after one year.[10] Van Gucht et al. reported that 66.2% of users exhibited tendencies to reduce or quit smoking after one year.[60] However, some international studies suggest that e-cigarettes are not effective for smoking cessation.[61]

Air quality measurements conducted in homes where e-cigarettes are used revealed higher nicotine levels compared to smoke-free homes, raising concerns about passive exposure.[11]

Studies on e-cigarettes, their use, and effects

When examining the international literature closely, it is evident that the number of scientific studies on electronic cigarettes is limited. These studies can be categorized into three groups:

1- Survey studies,

2- Clinical observational studies conducted on e-cigarette users that evaluate the effects of usage through various measurement methods and compare them with other forms of nicotine consumption,

3- Observational and interventional studies investigating the potential health threats posed by e-cigarettes.

1-Survey Studies: Studies on e-cigarette use primarily consist of surveys focusing on device usage characteristics, user perceptions, effects on tobacco cessation, and reported complaints related to use. Most of these surveys have

been conducted among male users residing in the United States, Canada, and Europe, with participants typically recruited via e-cigarette blogs and smoking cessation websites.[9] Between 38% and 45% of respondents reported using e-cigarettes to quit or reduce harm from tobacco smoking. Although 53% to 84% did not consider the product completely safe, they perceived it as less harmful compared to tobacco cigarettes.[14,39] The reported dependence levels were lower than for tobacco, ranging between 26% and 60%.[39] The most frequently reported adverse effects were throat irritation (25%–27%) and dry mouth (20%–26%); other symptoms included cough, headache, gastrointestinal complaints, and palpitations.[12]

One study found that throat burning was more prevalent among nicotine-containing e-cigarette users and tobacco smokers.[14] Smoking cessation rates ranged from 31% to 96%, while reduction rates varied between 25% and 92%.[14,39,62] Some studies reported a 70% reduction in tobacco craving associated with e-cigarette use.[12] In a 12-month follow-up, 6% of users relapsed to tobacco within one month and another 6% within one year, while 22% quit smoking within one month and 46% by the end of one year. Continuation rates of e-cigarette use were 93% at one month and 81% at one year. Usage prevalence doubled over one year, with rates reported as 7% in the UK and USA and 9.5% among Korean adolescents.[62] Awareness rates were 70%–75% in the USA, 54% in the UK, 40% in Canada, and 20% in Australia.[62] Between 45% and 85% of participants believed that e-cigarettes helped to quit smoking, 75% believed it helped to reduce smoking, 53%–80% considered it less harmful, and 26% viewed it as less addictive. Usage among children was negligible.[62]

The main limitations of these surveys include selection bias due to recruitment mainly from e-cigarette websites, low participation rates, differing results from unbiased platforms, inclusion of former e-cigarette users, and lack of a clear definition for smoking cessation.[9]

2-Clinical Observational Studies on E-Cigarette Users Evaluating Usage Effects Through Various Measurement Methods and Comparing with Other Forms of Nicotine Consumption:

There is a limited number of clinical studies assessing the impact of e-cigarettes on smoking cessation. In a prospective study by Bullen et al. the efficacy of e-cigarettes and nicotine patches in smoking cessation was found to be comparable, with reported side effects being minimal.[26] Nicotine-containing e-cigarettes reduced withdrawal symptoms and craving similarly to nicotine inhalers; their effect was greater than nicotine-free e-cigarettes but not statistically significant, and they were better tolerated.[26]

In a six-month follow-up study, significant reductions in cigarette consumption and a cessation success rate of 22.5% were observed among e-cigarette users who initially had no intention to quit smoking.[63] Studies conducted on psychiatric patients also reported decreases in cigarette use and cessation with e-cigarette use, with side effects generally mild and diminishing over time.[63]

Goniewicz et al. evaluated nicotine delivery in e-cigarettes, finding variability in nicotine content across products and generally lower nicotine release compared to cigarettes. Another study reported that nicotine-containing e-cigarettes reduced withdrawal symptoms and smoking urges more than placebo, with more pronounced effects in males. Nicotine e-cigarettes helped maintain cognitive performance over time, though no significant effect on attention was found.[39]

Dawkins et al. reported similar findings, demonstrating positive effects of nicotine-containing e-cigarettes on mood, physical symptoms, and prospective memory over time,

but no effect on event-based memory.[64] These results suggest the potential of e-cigarettes as nicotine replacement; however, their comparative effectiveness with other methods remains unclear. Reported side effects were mostly minor.[64]

3-Observational and Interventional Studies on the Potential Health Threats of E-Cigarettes:

In 2011, the U.S. Food and Drug Administration (FDA) published results of its analysis on e-cigarette contents, detecting very small amounts of tobacco-specific nitrosamines (TSNAs) in the cartridges of two leading brands, and diethylene glycol—a toxic substance to humans—in one of 18 cartridge solutions.[15] Additionally, nicotine amounts varied across products labeled with the same nicotine content, and trace amounts of nicotine were found in products labeled as nicotine-free. Cahn and Siegel, discussing these findings, emphasized that the TSNA levels found in e-cigarettes by the FDA were much lower than those in tobacco cigarettes and comparable to the total amounts present in the FDA-approved NicoDerm patch.[65] They also noted that although the presence of diethylene glycol is significant, it was detected in only one of the 18 solutions.

A study analyzing aerosols from 12 different e-cigarette brands and a reference medical nicotine inhaler investigated potential toxic and carcinogenic compounds (carbonyls, volatile organic compounds, nitrosamines, and heavy metals). These substances were extracted in solid or liquid forms from aerosols and analyzed using chromatographic and spectroscopic methods. The results showed, depending on the brand, that some toxic substances such as formaldehyde, acetaldehyde, acrolein, toluene, and nitrosonornicotine were present in amounts 9 to 450 times lower than in tobacco cigarettes and often comparable to the reference product. Another study identified particulate matter within e-cigarette aerosols and detailed methods for their detection and quantification.[66]

An investigation of the cartomizer liquid and aerosol, utilizing light and electron microscopy, cytotoxicity tests, X-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectroscopy, found toxic agents. Copper and tin were detected in the cartomizer liquid, with copper shown to be toxic to human pulmonary fibroblasts. The aerosol contained tin, silver, iron, nickel, aluminum, and silicate particles, many of which have the potential to cause respiratory stress diseases. Most detected elements (9 out of 11) were present at levels equal to or higher than those found in tobacco cigarettes. The authors stressed the need for further studies on the health effects of these substances on e-cigarette users and bystanders and emphasized improving quality control in e-cigarette design and manufacturing. In a cytotoxicity study analyzing 40 different e-cigarette cartridge liquids, only one brand showed cytotoxicity to human embryonic stem cells and mouse neural stem cells, while no cytotoxicity was observed in human pulmonary fibroblasts. Chemical analyses indicated that cytotoxicity was not related to nicotine but to the type and concentration of flavoring chemicals, highlighting the need for more detailed prenatal impact studies.[67]

A study assessing blood parameters found no changes related to active or passive e-cigarette use in smokers or nonsmokers. However, both active and passive tobacco cigarette use increased white blood cell, lymphocyte, and granulocyte counts for at least one hour.[67]

Pulmonary effects of e-cigarette use were studied, revealing that five minutes of e-cigarette use significantly increased total respiratory impedance (5 Hz) and flow respiratory impedance (5, 10, 20 Hz) compared to a control group using cartridge-free e-cigarettes.[68] Analyses controlling for baseline values showed significant decreases in exhaled nitric oxide (NO) levels and significant increases in respiratory impedance, resistance,

and total peripheral airway resistance. These findings indicate that e-cigarette use causes short-term adverse respiratory effects similar to tobacco cigarettes and highlight the need for long-term studies.

Passive exposure to e-cigarette vapor was investigated in a study where emissions generated in an 8 m^3 emission test chamber and exhaled mixtures in smaller chambers were analyzed. Compared to tobacco smoke, much lower amounts of volatile organic compounds (propanediol, propanetriol, diacetyl) and finer, lower-concentration particles were detected. Differences between vapor released into the air and exhaled breath content suggest possible deposition and evaporation mechanisms in the lungs. The study concluded that although passive e-cigarette exposure involves very small substance amounts, further research is needed.[11]

A controlled, repeated-measures study evaluated the cardiovascular effects of smoking tobacco cigarettes and using e-cigarettes with different nicotine levels in the same subjects. Plasma nicotine, carbon monoxide (CO) concentrations, and heart rate significantly increased within five minutes after tobacco cigarette smoking but showed no change with e-cigarette or non-combustible cigarette use.[69] Subjective effects measured over 60 minutes indicated that both tobacco and e-cigarette use reduced withdrawal symptoms, with greater effects observed for tobacco cigarettes. Overall, these studies suggest that while e-cigarettes are generally considered safer than tobacco cigarettes, they still pose potential health threats.

Despite the widespread global use of e-cigarettes as alternatives to tobacco smoking and their increasing popularity, scientific evidence regarding their efficacy for smoking cessation and health effects remains insufficient. The role of e-cigarettes in tobacco control is still uncertain.[26] Urgent research publications addressing these issues at individual and population levels are needed. Turkey has begun contributing to this field, at least through experimental studies.

According to the Truth Longitudinal Cohort study conducted in the United States between 2018 and 2019, there was a non-significant increase of 1.1% in daily tobacco use, from 14.6% to 15.7%. Data from the National Health and Nutrition Examination Survey (NHANES) showed that current and former e-cigarette users had a 30% higher likelihood of metabolic syndrome (MetS) compared to non-users.[34,70] E-cigarette use and dual use are associated with MetS. An 8-year longitudinal study of long-term, continuous e-cigarette users revealed significant changes in e-liquid flavors and strengths over time, with a tendency for nicotine dependence levels to decrease.

In the European Union's Eurobarometer study (2017); Among the reasons for using electronic cigarettes, the most frequently reported was to reduce or quit smoking (61%), followed by perceptions of being less harmful (31%), lower cost (25%), ability to use in places where smoking is banned (15%), availability of different flavors (12%), friends' usage (11%), and looking cooler (6%). In a study conducted in Germany among individuals aged 14 and older, reasons for use included curiosity (59%), quitting tobacco use (29.1%), using as a cigarette substitute (7.8%), and flavor and cost (2.1%). Among smokers in this study, the desire to quit was 46%, while among youth, curiosity was prominent at 73%.

Electronic cigarette use, which entered the United States market in 2006, has rapidly increased. In a systematic review by Fadus et al. e-cigarette use among high school students in the past 30 days increased from 1.5% in 2011 to 11.7% in 2017 and 20.8% in 2018. Among middle school students, use rose from 0.6% in 2011 to 4.9% in 2018.

As the use of e-cigarettes recommended for smoking cessation has become more widespread, research findings regarding health issues have also begun to emerge. Although toxic substances in e-cigarettes are reported to be 9 to 450 times less than in traditional cigarettes, carcinogenic substances remain present. The view that e-cigarettes are harmless to health is gradually declining. While long-term health effects caused by inhalation of propylene glycol/vegetable glycerin contained in e-cigarettes have yet to be fully explained, many studies mention systemic health problems.

The toxic effects of substances contained in e-cigarettes should not be overlooked.

It is also noted that e-cigarettes may cause numerous health problems.

In the FDA (Food and Drug Administration) study: In 2009, the international health authority FDA examined the cartridges of 18 different e-cigarette products from two companies available on the market.[71] The findings of this analysis were as follows:

- Known carcinogenic nitrosamines, also found in tobacco, were detected in half of the samples.
- Diethylene glycol, a substance known to be toxic to humans, was found at a 1% concentration.
- Anabasine, myosmine, and beta-nicotyrine—substances previously proven to be harmful to human health and also present in tobacco—were detected in most samples, although these compounds could not be demonstrated in the vapor of exhaled air.
- All samples labeled as nicotine-free contained low levels of nicotine.
- In nicotine-containing samples with identical nicotine amounts stated on their labels, nicotine concentrations ranged from 4.2 to 26.8 mcg/100 mL puff.

Additionally, various studies outside of the FDA reported the presence of certain harmful chemicals such as formaldehyde, ketones, mercury, and tetramethylpyrazine in e-cigarette aerosols. Although these substances were found at significantly lower levels compared to tobacco smoke, it was suggested that such low doses may not pose a substantial health risk.

Following these investigations, the FDA reported in July 2009 that e-cigarettes are not as harmless as claimed and that health warnings regarding these products were insufficient. Despite criticism of the FDA's findings by the e-cigarette industry and some researchers, these results heightened health concerns related to these devices. Conversely, some researchers argued that the concentrations of harmful substances in e-cigarettes are as low as one-millionth (1/1,000,000) of levels considered harmful to human health, suggesting that they cannot be deemed dangerous.

Discussion

The American Association of Public Health Physicians (AAPHP), In April 2010, the American Association of Public Health Physicians (AAPHP) stated that providing e-cigarettes to adult tobacco users posed no significant concern, suggesting that this approach could potentially save the lives of 4 to 8 million adults by preventing diseases related to smoking. However, they emphasized that these devices should be reclassified by the FDA from drug/device combinations to the tobacco products category. Additionally, AAPHP strongly opposed the sale of these devices to minors.[71]

Public Health Agency of Canada: In March 2009, the Canadian Health Agency reported that although e-cigarettes had been introduced to the market as a safer alternative to traditional tobacco products, they may lead to adverse effects such as nicotine poisoning or the initiation of nicotine addiction.[71]

Opposing Perspectives: Although some of the studies in the literature and reports from international health organizations have stated that e-cigarettes are harmful and not suitable for use, indicating that they carry similar health risks to conventional tobacco products[71], there are also studies supporting opposing views. According to these studies and researchers, although e-cigarette use cannot be described as completely harmless, it causes significantly fewer health side effects compared to tobacco use, and the current toxic content is considerably lower than that of traditional tobacco.[71]

To date, no e-cigarette has been approved for use as Nicotine Replacement Therapy (NRT). In addition to health concerns, the uncertainty about whether they contain nicotine suitable for therapeutic purposes has also played a role in this. The World Health Organization (WHO) has emphasized that, despite claims by manufacturers, e-cigarettes cannot be accepted as a "smoking cessation treatment" until sufficient research, including toxicity studies, has been conducted.[71]

Current Legal Status in Various Countries: Due to the relatively recent emergence of e-cigarette technology and the complexity of tobacco legislation and pharmaceutical policies, legal regulations regarding e-cigarettes remain insufficient in many countries.[71] Various legal approaches exist across European Union countries and U.S. states:

- In Finland, while the use of e-cigarettes is not prohibited, their sale and marketing are subject to strict regulations. Therefore, it is essential for e-cigarette users and retailers to closely monitor the current legal framework.
- In Germany, although it has been verbally suggested by the Minister of Health that nicotine-containing e-cigarettes would be banned, their sale and use remain legal.
- In Italy, the sale and use of e-cigarettes are legal; however, a law enacted in 2012 prohibits their sale to individuals under the age of 16.
- In the United Kingdom, the advertisement, sale, and use of e-cigarettes are permitted. They can also be used in public places. However, starting from June 2025, the sale of disposable e-cigarettes will be prohibited.
- In the United States, different states enforce different policies. In some states, there are no prohibitions, while in others—such as New Hampshire and Arizona—sales to minors are prohibited. In New York, sales to minors are also banned, and as of 2012, the use of e-cigarettes has been prohibited within 100 feet of public spaces and at the entrances of private schools.

Legal regulations on tobacco products in Türkiye

In Türkiye, the most comprehensive legal regulations regarding tobacco products (including cigarettes, waterpipes, and cigars) are outlined in two main legislative texts: Law No. 4207 on the Prevention and Control of the Harmful Effects of Tobacco Products and Law No. 4733 on the Regulation of Tobacco, Tobacco Products, and Alcohol Market.[71] A notable common feature of these laws is that they do not provide an exhaustive list of tobacco products by name, but instead apply to all products containing tobacco, regardless of form.

As a result, all restrictions imposed on traditional tobacco products—such as bans on sales to minors, advertising and promotion prohibitions, spatial usage limitations, and commercial trade restrictions—are equally applicable to electronic cigarettes (e-cigarettes).

In summary, since e-cigarettes are legally categorized as tobacco products in Türkiye, they fall under the advertising ban and, in accordance with Law No. 4207, cannot be sold on online platforms or shipped via cargo services. Moreover, a 2008 decision by the Ministry of Health classified e-cigarette cartridges as pharmaceutical products due to their high nicotine content, and e-cigarette devices as medical equipment, thereby excluding them from free trade channels.

Despite these regulatory measures, e-cigarette use is still observed in Türkiye, primarily due to illicit sales through online or other unauthorized means. However, thanks to the legislative efforts and effective enforcement of these policies, Türkiye serves as a successful global example in the regulation of e-cigarettes and the protection of public health from tobacco-related harm.

Conclusion and recommendations

At the beginning of the last century, cigarette smoking became an epidemic; however, over the past 50-60 years, global efforts have led to a decline in smoking prevalence worldwide. Following the introduction of the WHO Framework Convention on Tobacco Control and the MPOWER package, the number of smokers globally has decreased, thereby saving millions of lives. The annual number of smokers continues to decline. According to the report published after the ninth Conference of the Parties (CoP) held in November 2021, while there were 1.32 billion smokers worldwide in 2015, this number decreased to 1.30 billion in 2021, and it is projected to fall to 1.27 billion by 2025. The Western Pacific Region exhibits the highest smoking prevalence among men (45%), whereas the European Region has the highest prevalence among women (18%). The harmful effects of smoking are universally acknowledged; even the tobacco industry can no longer deny this fact. Based on the established harms of tobacco use and tobacco smoke, the tobacco industry founded the Foundation for a Smoke-Free World in 2017 and declared the development of the IQOS product to contribute to the formation of a "smoke-free world." The foundation's proposal advocates for the cessation of cigarette smoking and substitution with this product. Accordingly, the tobacco industry promotes IQOS as an alternative to cigarettes to retain approximately 1.3 billion smokers and conducts intensive marketing campaigns for these products, particularly targeting young people. It is a well-known fact that young users of these products often become cigarette-dependent shortly thereafter. Therefore, tobacco control efforts in the coming years are expected to shift focus from combating cigarette smoking to preventing the use of these novel products.[72]

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Ethical approval

This study has been approved by the Pamukkale University Non-Interventional Clinical Research Ethics Committee (approval date: 08.01.025, number: E-60116787-020-636220). Written informed consent was obtained from the participants.

Author contribution

Review conception and design: NMA; literature review: NMA, SP; draft manuscript preparation: NMA. The author(s) reviewed the results and approved the final version of the article.

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Conflict of interest

The authors declare that there is no conflict of interest.

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