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# E-SMOKING: EMERGING PUBLIC HEALTH PROBLEM?

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**Abstract**
E-cigarette use has become increasingly popular, especially among the young. Its long-term influence upon health is unknown. Aim of this review has been to present the current state of knowledge about the impact of e-cigarette use on health, with an emphasis on Central and Eastern Europe. During the preparation of this narrative review, the literature on e-cigarettes available within the network PubMed was retrieved and examined. In the final review, 64 research papers were included. We specifically assessed the construction and operation of the e-cigarette as well as the chemical composition of the e-liquid; the impact that vapor arising from the use of e-cigarette explored in experimental models *in vitro*; and short-term effects of use of e-cigarettes on users' health. Among the substances inhaled by the e-smoker, there are several harmful products, such as: formaldehyde, acetaldehyde, acroleine, propanal, nicotine, acetone, o-methyl-benzaldehyde, carcinogenic nitrosamines. Results from experimental animal studies indicate the negative impact of e-cigarette exposure on test models, such as ascytotoxicity, oxidative stress, inflammation, airway hyper reactivity, airway remodeling, mucin production, apoptosis, and emphysematous changes. The short-term impact of e-cigarettes on human health has been studied mostly in experimental setting. Available evidence shows that the use of e-cigarettes may result in acute lung function responses (e.g., increase in impedance, peripheral airway flow resistance) and induce oxidative stress. Based on the current available evidence, e-cigarette use is associated with harmful biologic responses, although it may be less harmful than traditional cigarettes. Int J Occup Med Environ Health 2017;30(3):329–344

**Key words:**
**Smoking, Nicotine, Literature review, E-cigarette, Electronic cigarette, Tobacco products**

## INTRODUCTION

The electronic nicotine delivery system called an "electronic cigarette" or "e-cigarette" has become widely popular, especially among young people [1,2]. It has been advertised in the mass media as a safer alternative to traditional cigarettes and as an aid to reduce or quit smoking.

E-cigarettes pose challenges for health policy and public health. It is a new source of nicotine, an addictive substance, which has a proven harmful effect on health [3]. In many countries, e-cigarettes are subject to different laws on tobacco cigarettes [4,5]. The sale of e-cigarettes to minors, its use in public places, and its qualification as

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a medical device or tobacco product should be regulated but these regulations vary by jurisdiction. In addition to this, despite what is portrayed in popular mass media and advertising, the impact of the long-term use of e-cigarettes on health is unknown. While this is true for long-term use, fortunately, there is a growing body of research investigating the short-term impact of e-cigarette use on health as well as evidence from experimental animal studies.

Electronic cigarettes are powered by a battery or accumulator device with a heating element that heats the fluid (the e-liquid) to a temperature of about 200–300°C to form an aerosol (vapor) which is inhaled into the lungs. To substitute visual and behavioral aspects of cigarette smoking, e-cigarettes are designed to look like traditional tobacco cigarettes [6]. There are 4 types of e-cigarettes: disposable; first generation-rechargeable cigarette-shaped; second generation pen-style, larger than a cigarette, with a refillable cartridge; third generation tank-style large-sized, rechargeable with manual switches, which may be easily modified [6,7].

The aim of this review is to examine the current state of knowledge about the impact of e-cigarette use on health focusing within the context of Eastern and Central Europe, regions with high smoking prevalence. As part of this process, we will:
– review the chemical composition of e-cigarettes and consider the theoretical potential of harm from these devices,
– review evidence from animal studies,
– review evidence from human based short term exposure studies and finally,
– describe the prevalence of e-cigarette use and behavior towards its use as a way of considering the potential burden of a problem.

As such, this review will include an examination of the construction and operation of the e-cigarette, the chemical composition of the e-liquid, the impact of vapor products arising from the use of e-cigarettes on laboratory experimental models *in vitro* and short-term effects of the use of e-cigarette use on the user's health.

## MATERIAL AND METHODS

To review the evidence, we made use of PubMed for our literature search and included articles published from January 2010 until May 2016. Combinations of following key-words were used: "electronic cigarette," "e-cigarette," "e-cigarettes," "e-cig," "electronic nicotine delivery system" with phrases from the four groups of studies: chemical composition (key words: aerosol, carbonyl compounds, indoor air quality, nicotine, e-liquid, vapor); animal experimental studies (key words: cytotoxicity, lung function, mice, cells); and human based short term exposure studies (key words: safety, health effects, toxicity, secondhand exposure); prevalence of use (key words: smoking, smoking cessation, adolescence, students, e-smoking, reasons for use).

From this search, a total of 1985 potentially relevant articles were identified. This number was reduced to 108 articles after screening titles and abstracts for relevance to the current review by two independent reviewers. The articles dealing partly or exclusively with health effects correlated to e-cigarette exposure were considered as a potentially relevant article. All studies were in English. After reaching a list of potentially relevant articles, the full text of each paper was appraised, with particular emphasis on the time and route of e-cigarette exposure, the characteristics of the population, the presence of a control group and study limitations. Additionally, reference lists from selected publications were searched to identify additional articles that may be relevant to the topic of this review. Case reports, articles that reported health effects caused by direct e-liquid exposure (without combustion), studies involving mental illness among the study group were excluded from further analysis. Although narrative reviews have more potential for bias than meta-analysis, we tried to be systematic and critical in our selection and appraisal of the articles.

In our review we have attempted to focus on evidence from Central and Eastern Europe. However, we found that there was a limited number of articles from this region. With the exception of Poland, where there were approximately 30 articles, each country had a maximum of 5 articles published. Originally we selected 51 articles. Following suggestions from experts in the field, we selected additional 13 articles resulting in a total of 64 publications, out of which 15 were from Central and Eastern Europe. Experimental studies evaluating exclusively the impact of e-smoking on health are listed in the tables of this review. This was done in order to more extensively present study characteristics and results in order to present the information from each study allowing the reader for a more thorough assessment of the current literature to draw interpretations and final conclusions.

## RESULTS

### Chemical composition of the e-liquid and created aerosol

E-liquids differ in their chemical composition, the content of flavoring substances, and nicotine content (0–24 mg) [8]. Most of them contain propylene glycol and/or glycerin, nicotine, water or ethanol, flavors, and other additives [8]. However, there are significant differences between the composition declared on the packaging and the composition resulting from a chemical analysis [8–10]. In particular, differences may occur in the contents of nicotine, where the differences may be greater than 100% [9]. The European Union (EU) Directive, that has been in force since May 2016, determines the maximum size of the e-liquid containers and limits the concentration of nicotine in e-cigarette liquids to 20 mg/ml [11]. Currently, there are about 8000 different flavors available for e-cigarettes [12]. Manufacturers offer newer and more diverse flavors like bubblegum, fruit, and chocolate, potentially to encourage young people to reach for the e-cigarette. Some e-smokers, likely due to financial issues and the desire to experiment with something new, are choosing to create homemade e-liquids. Also, there is a risk that the e-cigarette is used as a new tool of inhaling cannabinoids and other psychoactive substances [13].

Among the substances inhaled by an e-smoker, researchers have identified several harmful products including: formaldehyde, acetaldehyde, acroleine, propanal, nicotine, acetone, o-methyl-benzaldehyde, and carcinogenic nitrosamines [10,14,15]. E-cigarette use also results in the emission of particulate matter, which then increases the concentration in ambient air [16,17]. Despite the emission of these substances, emission of these substances was 6–450 times higher in the tobacco cigarette than in the e-cigarette [14,16]. There is some evidence suggesting that through the use of new generation e-cigarettes, where the user may adjust the voltage of the device, there is an increased generation of more harmful substances (e.g., formaldehyde) [18]. Jensen et al. examined the concentrations of formaldehyde generated by e-cigarettes featuring a variable-voltage battery [18]. In the case of low levels of e-liquid in the container and at high voltage (5 V), heating elements were overheated, resulting in excessive degradation of propylene glycol to formaldehyde [18]. The authors suggest that the e-smoker would be exposed to 5–15 times higher dose of formaldehyde as compared to a traditional smoker [18]. However, these trials were conducted in the laboratory, without human participation, and the voltage applied in the tests may be difficult to reproduce during the daily use of e-cigarettes [18,19].

Passive smoking phenomenon related to e-cigarette use is not the issue as important as it is with smoking tobacco. The vapor exhaled by the user influences only the environment but may contain: volatile organic compounds, 1,2-propanediol, nicotine, and ultrafine/fine particles [20–22]. It is suggested that the concentration of toxic substances to which the passive smoker is exposed, is on average 10 times lower than in the case of tobacco cigarette use [21,22].

**Evidence from experimental animal studies**

In order to identify the effect of e-cigarette exposure experimentally, several *in vitro* studies on mouse lung cells, human embryonic stem cells, mouse neural stem cells, human pulmonary fibroblasts, and in vivo mouse models have been performed (Table 1). The evidence indicates a negative impact of e-cigarette exposure in these experiments. Experimental studies were performed on mice or *in vitro* cell models exposed to e-cigarette vaping using a specially constructed "smoking-machine" which provided aerosol exposure [23–30]. However, studies differed in duration, exposure time, and nicotine content in the e-liquid making it difficult to compare the results. Despite this, studies have shown cytotoxic effects of e-cigarette vapor on cells but the level of cytotoxicity was dependent on the flavor of e-liquid [24,26–28]. Coffee and cinnamon flavored e-liquids were the most cytotoxic [24,27,28]. Some sweet flavors such as toffee, butter, milk or chocolate contain diacetyl and acetyl propionyl [31]. In comparison to other flavors, cherry flavored e-liquid is characterized by a higher content of benzaldehyde [32].

Exposure has been shown to induce oxidative stress, inflammatory responses in lung epithelial cells and in the mouse lung, to alter ciliary function and induce cytokine release in lung epithelial cells [23–25]. These changes may play a role in development of disorders occurring with chronic airway inflammation. Some authors have suggested that nicotine delivered by a e-cigarette acts on the nicotinic receptor and causes the influx of calcium into the cell which increases protein kinase C-alpha (PKC-α) and extracellular signal-regulated kinase (ERK) and activates a cascade of reactions [23] responsible for: inducting airway hyper reactivity, airway remodeling, mucin production and apoptosis, emphysematous changes, and increased airway resistance in response to methacholine [25]. These experiments help identify and understand the processes that occur in cells during the use of e-cigarettes. However, some authors who had investigated the impact of e-cigarette and cigarette smoking on mouse lungs, concluded that the effect of e-cigarette smoking was significantly lower as compared to the effect of cigarette smoking [29]. Results from one study carried out on cell lines of human tracheobronchial epithelium suggested that there were no significant changes in cell viability after e-cigarette exposure and the results were similar to the control group exposed to air [30]. Future research should be extended to further investigate the effects of e-smoking as a possible risk factor for the development of chronic respiratory diseases.

**Short-term impact of e-cigarette use on health**

Due to the fact that e-cigarettes have only been in the market for a decade, studies on the long term effects of e-smoking on health are not available. However, the short-term impact of e-cigarette use on health has been described in the literature (Table 2). The findings indicate that the use of e-cigarettes may result in short-term responses. Questionnaire-based assessment indicates that the use of e-cigarettes is responsible for mouth and throat irritation, dry cough [33], headache, nausea, dyspnea, and vertigo [1].

In experimental studies of smokers where e-smokers and control subjects were included, the acute effects of using an e-cigarette were compared. However, research protocols differed in terms of time of using the e-cigarette, amount of puffs taken, and nicotine content in the e-liquid. In the future, consistency between studies would allow for a more accurate comparison and interpretation of results.

An experimental study assessing the effect of short-term e-cigarette vapor exposure on normal epithelial cells and head and neck squamous cell carcinoma (HNSCC) cell lines revealed a reduction in cell viability and clonogenic survival as compared to untreated controls [34]. Even after one week, researchers noticed an induction of deoxyribonucleic acid (DNA) breakage and cell death. These findings suggest genotoxic and carcinogenic effects of e-cigarette use [34].

**Table 1.** The effect of e-cigarette exposure in experimental animal studies

| Author | Aim of the study | Study design | Summary |
|---|---|---|---|
| Geraghty et al. (2014) [23] | to assess the influence of the nicotine in e-cigarette exposure on the lungs | mice, 4 groups (PBS alone/vehicle alone/e-cigarette liquid 18 mg/ml/e-cigarette liquid 36 mg/ml)<br>all groups were exposed for 1 h daily for 8 days or 4 months | emphysematous changes<br>inducting airway hyper reactivity<br>inducting airway remodeling, mucin production and apoptosis<br>alters ciliary function in lung epithelial cells<br>induces cytokine release from lung epithelial cells; increased PKC-α and ERK activation in the lungs |
| Lerner et al. (2015) [24] | to assess the effect of short-term (3 days) exposure to e-cig aerosols on aspects of lung inflammation, oxidative stress, and redox physiology by measuring changes in glutathione levels in mice | e-cigarette (tobacco flavor containing 16 mg nicotine)<br>exposure using Teague smoking machine<br>mice received 5 h exposures per day for 3 successive days | induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung<br>the level of cytotoxicity depends on the flavors of e-liquid |
| Glynos et al. (2015) [25] | to compare the effects of e-cigarette vapor vs. cigarette smoke in the lungs of mice | 6 mice were exposed for 3 days or 4 weeks to air, cigarette smoke or e-cigarette vapor | increased airway resistance in response to methacholine<br>perturbs respiratory mechanics |
| Bahl et al. (2012) [26] | to compare the sensitivity of embryonic and adult cells to a range of e-cigarette refill products and examines the chemical characteristics of refill fluids | 41 e-liquids from 4 manufacturers,<br>3 types of cells: human embryonic stem cells, mouse neural stem cells, and human pulmonary fibroblasts | cytotoxicity was dependent on the concentration and the number of flavors contained in the e-liquid<br>most of the toxicity being due to flavor additives<br>cinnamon Ceylon was the only sample that was highly cytotoxic to all cell types<br>embryonic and neonatal stem cells were more sensitive to refill products than adult lung fibroblasts |
| Farsalinos et al. (2013) [27] | to evaluate the cytotoxic potential of electronic cigarette vapor from a variety of liquid samples on cultured cardiomyoblasts, and to examine whether higher wattage has any effect in their cytotoxic potential | a commercially available tobacco cigarette (0.8 mg nicotine),<br>20 commercially-available e-liquids (nicotine 6–24 mg/ml) | cinnamic e-liquid showed greater cytotoxicity than the other flavors<br>products of higher-voltage e-cigarettes caused a decrease in cell survival<br>evaluating differences in cytotoxic potential of EC samples quality and quantity of flavorings should be analyzed<br>most tobacco used product was cytotoxic; only one e-liquid sample (cinnamon) using food-approved flavoring was marginally cytotoxic |

**Table 1.** The effect of e-cigarette exposure in experimental animal studies – cont.

| Author | Aim of the study | Study design | Summary |
|---|---|---|---|
| Romagna et al. (2013) [28] | to evaluate the cytotoxicity of e-liquids compared to the effects of cigarette smoke | 21 commercially available e-liquids, monolayer-cultured mouse fibroblast | only vapor from coffee flavored e-liquid was cytotoxic on cultured fibroblast |
| Husari et al. (2016) [29] | to investigate the effects of e-cigarette vapor and cigarette smoke in an animal model | three groups: control, cigarette smoke, e-cigarette (liquid 18 mg/ml);<br>11 mice in each group; smoke generator; 3 consecutive days (2 sessions per day, 3 h exposition each) | exposure to e-cigarette vapor resulted in acute *in vivo* harmful effect on the lung, there was a significant increase in wet-to-dry ratio compared to the control group, but the highest W/D ratio was after exposure to cigarette smoke<br>albumin leak in bronchoalveolar lavage fluid was noticed in cigarette smoke group, this effect was not evident in the e-cigarette group<br>e-cigarette vapor exposure resulted in a significant increase of L-1β<br>cigarette smoke exposure resulted in a significant increase of IL-1β, IL-6<br>TNF-α expression, and oxidative stress<br>significant cell death after cigarette smoke did not observe after e-cigarette vapor |
| Neilson et al. (2015) [30] | to develop an *in vitro* cytotoxicity model for e-cigarette and cigarette aerosol exposure, using 3D reconstructed human airway tissue | highly differentiated *in vitro* 3D reconstructs of primary human tracheobronchial epithelium (EpiAirway™), Smoking Robot with exposure module: control group, cigarette, e-cigarette; exposure time up to 6 h | cell viability reduction dependent on time manner (up to 12% in 6 h) after cigarette smoke<br>there were no significant changes in cell viability after e-cigarette, results similar to the control group |

PBS – phosphate-buffered saline; PKC-α– protein kinase C-α; ERK – extracellular signal-regulated kinase; EC – e-cigarette; W/D – wet-to-dry ratio; L-1β – interleukin 1β; IL-6 – interleukin 6; TNF-α – tumor necrosis factor α; 3D – 3-dimensional.

**Table 2.** Acute effects of using an e-cigarette on human health

| Author | Aim of the study | Study design | Summary |
|---|---|---|---|
| Vansickel et al. (2010) [36] | to describe clinical laboratory methods that could be used for characterizing EC users' nicotine and CO exposure, cardiovascular response and ratings of tobacco/nicotine abstinence symptom suppression and product acceptability | study group – 32 smokers (≥ 15 cigarettes/day)<br>4 sessions (no cigarette/own cigarette/ e-cigarette (18 mg)/e-cigarette (16 mg)<br>10 puff every 30 s<br>after each session (after 5, 15, 30 and 45 min) participants completed a questionnaire on the subjective effects and blood samples were collected | the use of e-cigarettes did not cause significant changes in heart rate, plasma nicotine level and CO concentration<br>the opposite effect was observed after using tobacco cigarette |
| Vardavas et al. (2012) [47] | to investigate the influence of e-cigarette using for 5 min on respiratory mechanics and FeNO | study group – 30 smokers<br>experimental group used e-cigarette at 5 min in any way, the control group used the e-cigarette without cartridge | in group of healthy smokers, after 5 min use of e-cigarette was noted increase in impedance, peripheral airway flow resistance and oxidative stress |
| Schober et al. (2014) [17] | to analyze the levels of e-cigarette pollutants in indoor air and monitored effects on FeNO release and urinary metabolite profile | 9 adult volunteers, the study was carried out in a room (size was 18 $m^2$ and its volume 45 $m^3$)<br>subjects were asked to give spot urine before each exposure; exhaled CO and FeNO were measured | rise of FeNO in 7 of 9 cases<br>significant increase of nicotine and cotinine levels in urine samples of subjects who consumed e-cigarettes with nicotinic liquids |
| Farsalinos et al. (2014) [37] | to examine the immediate effects of electronic cigarette use on LV function, compared to the well-documented acute adverse effects of smoking | 36 healthy heavy smokers, before and after smoking 1 cigarette<br>40 electronic cigarette users before and after using the device with nicotine concentration (11 mg/ml) for 7 min | echocardiography examination has shown no effect of e-smoking on heart function; burning tobacco cigarette resulted in delayed relaxation of LV |
| Etter (2016) [38] | to assess change over time in saliva cotinine levels in experienced vapers | 98 formed smokers, using e-cigarette daily, follow-up – 8-month later participants collected saliva samples | cotinine levels were similar to levels usually observed in cigarette smokers<br>follow-up concentration of nicotine in their e-liquids decreased, but consumption of e-liquid increased (in order to maintain their cotinine levels constant) |
| Zarobkiewicz et al. (2016) [1] | to assess subjective symptoms indicated by the e-cigarette users | self-reported questionnaire | headache, nausea, dyspnoea, vertigo |

**Table 2.** Acute effects of using an e-cigarette on human health – cont.

| Author | Aim of the study | Study design | Summary |
|---|---|---|---|
| Polosa et al. (2014) [33] | to assess subjective symptoms indicated by the e-cigarette users | 24-month prospective observational, adult smokers (≥ 15 cigarettes/day) who were not keen to quit smoking at the time of recruitment or in the forthcoming 30 days | mouth irritation, throat irritation, and dry cough |
| Chorti et al. (2012) [21] | to assess and compare the acute and short term effects of e-cigarette and tobacco cigarette active and passive smoking on lung function | 15 smokers, evaluation effects of active and passive e-smoking | active use of an e-cigarette: cotinine increased; $FEV_1$/FVC unchanged<br>passive use of an e-cigarette: cotinine increased; $FEV_1$/FVC reduced<br>smoking tobacco cigarette: increased cotinine, increased CO; decreased $FEV_1$/FVC |
| Yu et al. (2016) [34] | to evaluate cytotoxicity and genotoxicity of short and long-term e-cig vapor exposure on epithelial cell lines, and to assess the influence of e-cigarette smoking on pathogenesis of HNSCC | normal epithelial cells (HaCaT) and head and neck squamous cell carcinoma cell lines (UMSCC10B, HN30) exposed to nicotine-containing and nicotine-free vapor from two e-cig brands; period range from 48 h to 8 weeks | increased cell death for all cell lines, independently of nicotine content (5-fold growth of cell death after nicotine-free vapor, and 10-fold increase after nicotine vapor)<br>increased (up to 1.5-times) in DNA strand breaks after exposition (even after one-week) on nicotine and nicotine-free e-cig vapor<br>reduced cell viability and clonogenic survival<br>increased rate of apoptosis and necrosis<br>all results were significant, regardless of nicotine content in e-liquid |

EC – e-cigarette; CO – carbon monoxide; FeNO – fractional exhaled nitric oxide; LV – left ventricular; $FEV_1$/FVC – forced expiratory volume in 1 s/forced vital capacity; HNSCC – head and neck squamous cell carcinoma; HaCaT – spontaneously transformed immortal keratinocyte cell line; UMSCC10B – head and neck squamous cell carcinoma cell line derived from a metastatic lymph node; HN30 – head and neck squamous cell carcinoma cell line derived from a primary laryngeal tumor; DNA – deoxyribonucleic acid.

Active and passive e-cigarette usage were not found to increase white blood cell count, lymphocyte count, and granulocyte count [35]. For comparison purposes, in the tobacco cigarette smoking group there was an increase in the count of all 3 components of blood cell counts [35]. The use of e-cigarettes has not been shown to cause significant changes in heart rate, plasma nicotine levels, or carbon monoxide (CO) concentration [17,36]. The opposite effects were observed among tobacco cigarettes smokers [17,36]. Echocardiography showed no effect of e-smoking on heart function while smoking a tobacco cigarette resulted in delayed relaxation of left ventricular (LV) [37]. E-cigarette usage caused significant increase in biological levels of nicotine and cotinine [17,38–40]. In some cases, the results were similar to levels typically observed among cigarette smokers. Etter [38] investigated the level of saliva cotinine in daily e-cigarette smokers. Their evidence suggests that mean cotinine levels are similar (281–310 ng/ml [38], 322 ng/ml [39], 373 ng/ml [40]) to levels previously observed among traditional cigarette smokers (245 ng/ml [41], 300 ng/ml [42], 338 ng/ml [43]). Schober et al. observed a significant increase in cotinine and nicotine levels in urine samples of e-cigarette smokers who used nicotinic e-liquids [17]. Mean cotinine in urine of active smokers and active users of e-cigarettes were found comparable [44]. Passive smoking and passive vaping led to comparable cotinine levels in serum of bystanders [45,46].

Short-term, acute respiratory responses were found among healthy smokers [17,21,47]. After 5 min of use of an e-cigarette, lung impedance, peripheral airway flow resistance, and oxidative stress increased [47]. Another study also showed that after e-smoking, fractional exhaled nitric oxide (FeNO) level increased for 7 out of 9 cases [17]. In one study, passive e-cigarette use was associated with reduction in forced expiratory volume for 1 s/forced vital capacity ($FEV_1$/FVC) while during active e-cigarette use, there were no changes in $FEV_1$/FVC [21]. In some cases, the effect observed after using an e-cigarette is smaller as compared to the use of tobacco cigarettes. However, the findings prove poor repeatability between the studies. The main limitations of the published evidence include small sample sizes, inconsistent content of nicotine in the e-liquid, and focus on the short-term impact of e-cigarette use on health. The letter point is the prelude to the discussion on long-term effect of e-cigarette smoking on human health. This topic needs further investigation.

**The frequency of the use of e-cigarettes in the population, attitudes, motivations**

E-cigarettes are advertised in the mass media as a safer alternative to traditional cigarettes which, thanks to the absence of combustion, is less toxic than tobacco cigarette exposure. E-cigarette use has become increasingly popular, especially among the young [2,48]. The unknown long-term impacts of e-cigarette use justify the view that regulations should be imposed on the sale of e-cigarettes, which should be monitored, prohibited for minors, and advertising should be limited until the evidence related to health is more clear [2,49–51].

Data from the 2012 Eurobarometer 385 survey [48], which included a population of 26 566 young adult smokers from 27 countries, indicated that 20.3% had ever used an e-cigarette overall. Young people from Central and Eastern Europe declared that they used e-cigarettes more often in comparison to the EU average. Estimates differ between countries: 34.3% in Czech Republic, 31.1% in Bulgaria, 31.0% in Poland, 22.3% in Hungary, 22.3% in Estonia, 22.2% in Romania, 8.8% in Italy, 10.9% in Spain, 11.5% in Belgium, 12.4% in Sweden, and 13.7% in Austria [48]. E-cigarette use was most popular in Denmark (36.3%) and the least popular in Slovakia (7.9%) [48]. National surveys show that 31.5% of Polish university students had ever used an e-cigarette [1]. Current use of e-cigarettes was declared by 8.3% of students, with a significant difference between students of non-medical universities and medical universities (12.4% and 4.4%, respectively) [1]. Among adolescents (15–19 years) there was an increase in the frequency of e-cigarette use [2]. Comparing the data from the years 2013–2014 to the data from 2010–2012, 62.1% (in 2013–2014) vs. 16.8% (in 2010–2012) had ever used e-cigarettes [2,52]. The percentage share of current users of e-cigarettes increased from 5.5% to 29.9% [2,52]. The use of both types of a cigarette (dual-users) increased from 3.6% to 21.8% [2,52]. In the same study, the current use of cigarettes was declared to be 38.0% [2].

Based on the data obtained from adolescents in Poland, Goniewicz et al. suggest that the e-cigarette does not displace a tobacco cigarette because not only is the e-cigarette prevalence growing but also the frequency of use of e-cigarettes is higher [2]. Dual users compared to exclusive e-cigarette users use both types of cigarettes more often and are exposed to higher nicotine dose, which may suggest a greater nicotine addiction in this group [2,53]. Most dual users initially smoked tobacco cigarettes and then opted for the e-cigarette [53]. However, in a group of dual users, 15.7% declared that e-cigarettes were the first product they had tried [53]. During an 8-month observation of long-term daily users of e-cigarettes, the concentration of nicotine in their e-liquids decreased but consumption of e-liquid increased which led to maintaining their cotinine levels indicating the strength of nicotine dependence.

Data from the Czech Republic obtained for a group of 1738 adult smokers indicates that 50% has ever used an e-cigarette [54]. Current use of e-cigarettes was declared by 9.5% of responders. As a reason for using e-cigarettes, 39.5% of e-smokers indicated a desire to reduce the use of tobacco cigarettes while 28% had decided to use e-cigarettes because they may use it in places where conventional cigarettes are prohibited. In a group of persons who have ever used e-cigarettes, 38% were disappointed after the first experience with an e-cigarette [54].

The study conducted on a sample of 826 undergraduate students at two Hungarian universities showed that 24.9% of students (24,3% medical and 25.3% non-medical) had ever used an e-cigarette [55]. Moreover, 11% of students who had never tried e-cigarettes had declared their willingness to try e-cigarettes in the near future. In this study, fewer than 1% of students reported current use of e-cigarette [55].

In many studies involving students, the most common reasons to choose the e-cigarette were: hanging-out with friends, partying, before going to the bed, and stressful moments [1]. Motivation to start e-smoking was to quit or reduce smoking tobacco, the possibility to use in public places, health considerations, and financial concerns [1,54–57].

The survey performed for a group of Parisian school children (12–19 years old) revealed that nearly 10% of e-cigarette experimenters were not traditional cigarette smokers [58]. The predictors of e-cigarette experimentation from this study included older age, smoking of a friend or brother, current cigarette or shisha smoking, and, somewhat paradoxically, the prohibition to smoke by parents [58]. Results from a study performed in the United States (US) among working adults showed that 3.8% of this group were current e-cigarette users [59]. The highest prevalence of e-smoking (5.1%) was among young adults (18–24 years old) [59]. Workers in the accommodation and food services industry had the highest prevalence of e-cigarette use (6.9%) in contrast to workers in education services with the lowest e-cigarette use prevalence (1.8%) [59].

One of the main reasons for deciding to use e-cigarettes is an attempt to reduce amount of smoking traditional cigarettes and some studies discuss that aspect [49,60]. In one trial, middle-aged, high dependent smokers who were motivated to quit smoking were divided into 3 groups: 289 were using nicotine (16 mg) e-cigarettes; 73 people used e-cigarettes without nicotine; 295 investigated used 21 mg nicotine replacement therapy (NRT) patches [60]. All the participants were supported by behavioral therapy. After 6 months, the abstinence of tobacco cigarettes

was measured using a self-reported questionnaire and confirmed by measuring exhaled carbon monoxide. In the group of e-cigarette users, 7.3% stopped smoking as compared to 5.8% of NRT users and the difference was not statistically significant [60]. In another trial, middle-aged, high dependent smokers who were not motivated to quit smoking were divided into 3 groups and completed the intervention over 12 weeks [61]. Groups differed in exposure time and nicotine content in the e-liquid [61].
Follow-up was performed after 52 weeks. The highest smoking cessation rate (13%) was obtained for the group which used e-cigarette with the highest nicotine content [61]. All e-cigarette users had lower smoking cessation rates (13%, 9%, 4%, respectively, as compared to placebo (9–15.6%) in leading research on the effectiveness of NRT, bupropinon and varenicline in smoking cessation [62,63]. Based on it, there is not enough conclusive evidence proving that e-cigarettes constitute effective method of aiding smoking cessation.

**Position of leading health organizations on e-cigarettes**

According to the World Health Organization, there is not enough evidence that smoking e-cigarettes is an effective method of aiding smoking cessation [49]. With the objective of combating nicotine dependence, it is recommended to use tested and approved nicotine replacement therapy [49]. In the absence of conclusive evidence of safety and the health impact of the use of the e-cigarette, it is recommended that there should be restrictions on advertising of e-cigarettes, especially e-liquids of fruit and sweet flavors which are particularly likely to encourage young people to start using the e-cigarette. The World Health Organization also indicates that it is necessary to prohibit the sale of e-cigarettes to minors [49].
A similar position has been agreed upon as the Forum of International Respiratory Societies (FIRS), which indicates that until clear data on the safety and health impact of e-smoking is available, e-cigarettes should be restricted or banned [50]. The Forum of International Respiratory Societies also warns that the growing popularity of e-cigarettes may increase the social acceptance of smoking and nicotine addiction, which is a significant public health problem [50]. The American Heart Association and European Respiratory Society points out that the market of e-cigarettes should be closely monitored, and based on scientific evidence there should be a decision to regulate and determine the legal status of the e-cigarette [50,51]. Similar conclusions were reported by Neuberger who warned against e-cigarettes in the initial Central European review on this subject, where the author was comparing e-cigarettes to a "wolf in sheep's clothing" [64].
The European Union in the Tobacco Products Directive (2014/40/EU) indicates that e-smoking is a major public health problem because e-cigarettes simulate smoking behavior and social approval for smoking [11]. It notes that it may lead to experimentation with other products containing nicotine. The EU also notes that there is no evidence of the influence of long term e-cigarette use on public health. The EU Directive sets rules on packaging and labeling. Its purpose is to have the actual chemical composition declared and be consistent with the true value and reduce nicotine content in the e-liquid to 20 mg/ml, which will be adequate for the majority of vapers [11]. The directive came into force in the Member States on 20 May 2016.

## CONCLUSIONS

Smoking e-cigarettes is becoming an increasingly popular habit and in some populations the frequency of their use is growing steadily. The prevalence of e-cigarette use is higher among the youth from Central and Eastern Europe compared to other countries in Europe. The analysis of chemical composition of e-cigarette vapor indicates the presence of toxic and harmful substances, such as: formaldehyde, acetaldehyde, acroleine, propanal, nicotine, acetone, o-methyl-benzaldehyde, carcinogenic nitrosamines, fine and ultrafine particulate matter. Exposure to these substances depends on the type of e-liquid flavor as well as heating conditions and may lead to various respiratory disorders including symptoms of cough and shortness of breath, irritation of upper respiratory airways, lung function impairment, and even diseases such as bronchiolitis.

Results from animal experiments indicate the negative impact of e-cigarette exposure on biological processes including cytotoxicity, oxidative stress, inflammation, airway hyper reactivity, airway remodeling, mucin production, apoptosis, and emphysematous changes. Findings provided by human studies show the short-term impact of e-smoking on health and the convincing data points to such disorders as changes in lung function (e.g., increase in lung impedance, peripheral airway flow resistance) and involvement of the mechanism of oxidative stress. Although the current state of knowledge supports the view that e-smoking poses smaller health risk as compared to tobacco smoking, it is too early to conclude that smokers have an access to a safer substitute of tobacco use. Both habits, tobacco smoking and e-smoking are associated with apparent health risks even if the latter seems to be smaller in terms of the available evidence. Against this argument it is obvious that some preventive measures have been already discussed and apart from research needs there is a move towards regulations regarding advertising and the sale of e-cigarette to minors. On the other hand, e-cigarettes may be considered or even recommended as a safer alternative to tobacco smoking, which is why there is a need to promote proven smoking cessation measures, including pharmacological therapies.

Accumulated evidence regarding the impact of e-smoking on human health shows several gaps and this is understandable, given a short history of the habit. Future studies will provide more information about the relationship between short-term and long-term consequences of e-smoking, particularly from the epidemiological point of view. Nevertheless toxicological characterization of personal exposures generated by e-smoking and already available findings from animal and human studies justify the view that e-smoking is an emerging public health priority and as such requires more actions in terms of research and health promotion, both leading to sound public health recommendations.

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