



## **Electronic Cigarettes – An Overview – Supplement March 2014**

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Since the publication of the report “Electronic Cigarettes – An Overview” of the German Cancer Research Center several articles on e-cigarettes have been published. This supplement will give a brief overview on these new articles.

This supplement follows the structure of the report “Electronic Cigarettes – An Overview” and adds information wherever new studies have been conducted. Topics without new references will not be treated.

## **Erratum:**

Electronic cigarettes – an overview, page 11, conclusions. Bullet point 2:  
“Glycerine may cause lipoid pneumonia on inhalation.”  
This sentence has to be deleted.

## 2 Product Characteristics

### 2.3 Variations in aerosol production and nicotine levels

#### ■ Evidence in 2013:

Different e-cigarette brands produce aerosols of varying density and aerosol density frequently declines during use. There is also substantial variability in the efficacy of nicotine delivery from the liquid into the aerosol, resulting in strong variations in nicotine levels in the aerosol of electronic cigarettes. The nicotine level in aerosol is influenced by power supply of the device and puff duration.

Most of nicotine is delivered during the first 150–180 puffs, with 21 percent to 85 percent of nicotine being vaporized from the liquid, depending on the product. Only few devices deliver nicotine consistently over a larger number of puffs. Efficacy of nicotine vaporization varies not only between brands but also within brands from one use to the next.

#### ■ New findings in 2013/2014:

Still there are great differences in how much of the nicotine of the cartridges is vaporized by different devices. In a test of five popular e-cigarettes depending on the brand 10 to 81 percent of nicotine present in the cartridges was vaporized during 300 puffs executed by a smoking machine. Most of the tested e-cigarettes

delivered nicotine consistently over 300 puffs.<sup>40</sup>

In a study with 14 experienced e-cigarette users there was only a weak correlation between the number of puffs taken and the plasma nicotine concentration. It is not clear whether these differences are the result of an inconsistent nicotine vaporization of the devices or a different puffing technique of the users.<sup>22</sup>

Often, liquids have alkaline pH, which enhances mucosal nicotine absorption<sup>46</sup>.

### 2.4 Deficiencies in declaration of liquid ingredients

#### ■ Evidence in 2013:

For some liquids the nicotine content declared on the bottle differed markedly from the effective nicotine in the liquid. Some bottles contained more and some less nicotine than declared.

#### ■ New findings in 2013/2014:

There is still debate on the nicotine content and the nicotine declaration on the bottles. In two studies, for most of the liquids analysed, the nicotine content and declaration corresponded quite well<sup>31,36</sup>. Other groups found marked differences between measured and declared nicotine concentrations; in several cases the cartridges contained more nicotine than declared<sup>6,40,46</sup>.

## 3 Health Effects

### Cytotoxicity

#### ■ Evidence in 2013:

No tests on the cytotoxic potential of liquids were available.

#### ■ New findings in 2013/2014:

Several tests on the cytotoxicity of liquids have been conducted. They show that there is high variability between brands as well as in-brand: Some liquids are cytotoxic to cultured cells, some liquids are not. The cytotoxic effect appears not to be related to nicotine, but to the flavours used or to tin present in the fluid.<sup>3,33,63,75</sup>

### 3.1 Potential health risks from ingredients

The main ingredients of e-cigarettes (propylene glycol, glycerine, flavours) have been approved for use in food, but this does not necessarily mean that they are also safe when they are repeatedly inhaled over a prolonged period of time – as they are when used in electronic cigarettes.

#### 3.1.3 Nicotine

#### ■ Evidence in 2013:

In first-time users of electronic cigarettes blood nicotine levels increase up to 3.5 ng/ml. Experienced e-cigarette users show blood nicotine levels between 10 and 15 ng/ml.

#### ■ New findings in 2013/2014:

In experienced e-cigarette users a plasma nicotine concentration of about 7 ng/ml can be achieved 10 minutes after a 10 minute e-cigarette session using a liquid with 18 mg/ml nicotine; at the

end of a 60 minute ad libitum session plasma nicotine peaked at approximately 14 ng/ml. There were large interindividual differences in maximum nicotine levels (14 subjects, only of 7 complete sets of blood). It is not clear whether these differences are caused by inconsistent nicotine vaporization of the devices or different puffing technique of the users<sup>22</sup>. New-generation products deliver nicotine faster and in higher amounts than first-generation products<sup>36</sup>. In experienced e-cigarette users cotinine levels in saliva are similar to those in smokers<sup>29</sup>. Non-users present in a room, where e-cigarettes are consumed, may absorb the nicotine released with the aerosol into the air<sup>38,65</sup>.

### Nicotine poisoning

#### ■ Evidence in 2013:

One case of a possible infant death secondary to choking on an e-cigarette cartridge had been reported to the U.S. Food and Drug Administration (FDA).

#### ■ New findings in 2013/2014:

The number of adverse effects due to e-cigarettes has markedly increased since 2009. About half of the adverse effects occur in children. Most are due to unintended exposure, followed by normal use or dermal exposure. Clinical symptoms appear to be caused by nicotine overdose and include nausea and vomiting, headache, dizziness, throat irritation, agitation, ocular irritation, dyspnea, confusion and palpitations. Adverse effects appear to be transient and unlikely to result in serious toxicity.<sup>15,56</sup> Intentional poisoning has been reported, both non-fatal and fatal; in the fatal case the person is supposed to have injected e-cigarette liquid in suicidal intention<sup>67,71</sup>.

### 3.1.4 Cancer-causing substances (carcinogens)

#### ■ Evidence in 2013:

In some liquids cancerogenic substances as nitrosamines have been detected in low amounts, and in aerosol formaldehyde, acetaldehyde, acrolein, nickel and chromium have been detected in low amounts. Formaldehyde and acrolein were only found in aerosol of glycerine-containing liquids; they probably form upon heating of glycerine.

#### ■ New findings in 2013/2014:

In a Korean study investigating 225 replacement liquids purchased during July 2011 to June 2012, in all liquids low amounts of formaldehyde and acetaldehyde have been detected<sup>50</sup>. In a liquid made in Italy have been detected low amounts of acetaldehyde, formaldehyde, crotonaldehyde, the tobacco-specific nitrosamine NNK, heavy metals and arsenic<sup>36</sup>.

### 3.2 Side effects

#### ■ Evidence in 2013:

Side effects of e-cigarette use have been reported to include mouth and throat irritations as well as dry cough, dizziness and nausea, with symptoms subsiding over time. Data on the impact of e-cigarette use on pulmonary function are contradictory.

Potential health consequences of long-term use of e-cigarettes are missing, because the products started being marketed only a few years ago.

#### ■ New findings in 2013/2014:

E-cigarette use provokes several health symptoms. Most health effects appear in the respiratory tract, mouth and throat, the neurological and sensory systems. About four times more negative than positive symptoms (as improved smell or breathing) are reported. Negative symptoms include cough, mouth irritations, eye irritations, muscle pain, chest pain, skin irritations, headaches, dizziness, nausea, sleepiness, sleeplessness, gum and nose bleeding<sup>36,44</sup>. Serious symptoms as asthma attack or increased blood pressure are rare. Some symptoms as vomiting, nausea and changes in heart rhythm may be caused by nicotine overdose. Others, such as anxiety and depression may relate to

nicotine withdrawal.<sup>44</sup> Sore throat and cough may be present independently of nicotine content<sup>70</sup>.

Vaping one single e-cigarette independently of nicotine content may impair lung function in never smokers as well as in healthy smokers and smokers with airway disease<sup>57</sup>.

Neither active e-cigarette use nor passive exposure to e-cigarette aerosol has any influence on several inflammation markers (IL-1 $\alpha$ , IL-1 $\beta$ , IL-2, IL-4, IL-6, IL-8, IL-10, vascular endothelial growth factor, TNF $\alpha$ , monocyte chemotactic protein-1, EGF)<sup>69</sup>.

### 3.3 Improvement of acute tobacco-related health problems

#### ■ Evidence in 2013:

Health improvements (less irritation of the throat, improved breathing and body fitness) reported by many users after switching to electronic cigarettes are probably attributable to reduction in smoking-related health damage. These users have presumably cut down or even quit smoking.

According to a case study, a patient suffering from chronic idiopathic neutrophilia returned to normal white blood cell counts and inflammatory factors after smoking cessation with the aid of an electronic cigarette. This observation is supported by a study with 15 electronic cigarette users, which found that the use of electronic cigarettes had no impact on white blood cells.

#### ■ New findings in 2013/2014:

In 51 smokers, the smoking of two cigarettes containing 0.7 mg nicotine decreased the elasticity and elevated the stiffness of the ascending aorta. In 57 ex-smokers, using an e-cigarette containing 18 mg/ml nicotine for 10 minutes had no effect on the elasticity of the ascending aorta.<sup>37</sup>

In a small sample of 13 smokers, the replacement of cigarettes by e-cigarettes (glycerine based liquid, 0.018 mg/ml nicotine as indicated by the authors of the study) for two weeks significantly reduced carboxyhaemoglobin (COHb) levels in blood<sup>72</sup>.

Health benefits reported by 111 vapers who completely substituted smoking by e-cigarettes include improved exercise capacity (in 76.6 % of the subjects), improved olfactory and gustatory senses (in 81.9 % of the subjects), less morning

cough (in 58.6 % of the subjects), better sleep (in 22.3 % of the subjects)<sup>35</sup>.

### 3.4 Indoor air pollution

#### ■ Evidence in 2013:

The aerosol of e-cigarettes contains large amounts of propylene glycol, the main ingredient of the liquids, as well as nicotine, flavours, liquid particles of less than 2.5 µm (PM<sub>2.5</sub>) diameter, tobacco-specific nitrosamines, volatile organic compounds, acetone, formaldehyde, acetaldehyde, benzo(a)pyrene and PM<sub>2.5</sub> as well as silicate and various metal particles. There may be differences in aerosol composition between products. The levels of most substances measured are lower in the mist of electronic cigarettes than in conventional cigarette smoke, however, if several people in a room are using electronic cigarettes at the same time, we have to assume that this results in considerable indoor air pollution due to accumulation.

Particle size in aerosol is between 100 and 600 nanometres and hence comparable to that of particles found in tobacco smoke of conventional cigarettes

#### ■ New findings in 2013/2014:

Several new studies confirm that e-cigarette use in indoor rooms impairs air quality, however to a markedly lesser extent than conventional cigarettes. After vaping nicotine, particulate matter, flavours as menthol and vanillin as well as small amounts of carcinogenic substances can be detected in the room air, but in much lower amounts than produced by conventional cigarettes<sup>20,65</sup>. The particle size distribution of particulate matter is similar to conventional cigarettes; the particle number increases with higher nicotine content, but is not related to flavour<sup>39,45</sup>. In another study particle size was bigger in e-cigarette aerosol than in smoke of conventional cigarettes and their half-life time in air was much shorter than for cigarette smoke. However, in aerosol exhaled by users, particle size corresponded to particle size in cigarette smoke. Moreover, the deposition of aerosol particles in the Alveoli did not differ from tobacco smoke.<sup>8</sup> These studies suggest that e-cigarette particles of e-cigarette

aerosol may be deposited deep in the lung and justify health concern<sup>39</sup>.

In aerosol of liquids several metals such as tin, nickel and chromium have been found. The nature of substances produced and their amount are likely to depend on engineering features of the e-cigarette, such as battery power, heating temperature or the type of the heating element.<sup>38,39,64,65,75</sup>

Nicotine may be absorbed by bystanders<sup>38,65</sup>.

Relying on data of studies investigating liquids and aerosols of e-cigarettes, Burstyn uses occupational threshold limit values (TLVs) to evaluate the potential risk of potentially hazardous substances in e-cigarette aerosol. He concludes that there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However the aerosol (composed of declared ingredients as propylene glycol and glycerine plus contaminants) may lead to exposures that may cause concern.<sup>12</sup> Nevertheless, the use of toxicological exposure limits for passive vaping is questionable: First, for carcinogenic substances – as they have been detected in low amounts in e-cigarette aerosol – no upper limits can be given below which these substances would be harmless. Second, threshold limit values are fixed for single substances and cannot be applied to mixtures of different substances as e-cigarette aerosol. Third, threshold limit values assess health effects for exposure at workplaces that are generally much higher; they do not consider exposure to sensitive groups, such as allergic people or people suffering from chronic diseases or children. Fourth, voluntary inhalation of vapour differs significantly from involuntary exposure to substances at workplaces.<sup>24</sup> The International Union Against Tuberculosis and Lung Disease states in its position statement on e-cigarettes that “adverse health effects for third parties exposed (second-hand exposure) cannot be excluded because the use of electronic cigarettes leads to emission of fine and ultrafine inhalable liquid particles, nicotine and cancer-causing substances into indoor air.”<sup>4</sup>



## 4 Product Awareness and Market Development

### Product awareness

#### ■ Evidence in 2013:

A large portion of the population is aware of electronic cigarettes. Awareness of electronic cigarettes is particularly high among smokers. Most adolescents and young adults are aware of electronic cigarettes.

#### ■ New findings in 2013/2014:

Awareness of e-cigarettes has increased in the last years: In the US in 2010 only about 40 percent of adults had ever heard about e-cigarettes, in 2011, in a group of 244 US students 71 percent knew about e-cigarettes, and in 2013 they were known by 86 percent of adults<sup>13,68</sup>. In 2013 in the UK 91 percent of adult smokers and 71 percent of the non-smokers have heard of e-cigarettes. Among children aged 11 to 18 two thirds knew e-cigarettes and 83 percent of youth aged 16 to 18<sup>1</sup>. E-cigarettes mostly are associated with positive sentiments<sup>55</sup>.

### Market development and marketing

#### ■ Evidence in 2013:

Sales have grown strongly over recent years. E-cigarettes are mostly sold via internet. E-cigarette companies are small, but Big Tobacco starts taking over e-cigarettes. There is advertising for e-cigarettes in internet and TV.

#### ■ New findings in 2013/2014:

Marketing for e-cigarettes is evolving. In the US, e-cigarettes are primarily advertised through print, television and E-mail<sup>61</sup>. In Europe, e-cigarette companies as Red Kiwi, E-Lites and cigg-e started sponsoring sports<sup>5,17,60</sup>. In 2013 in London about half of the stores selling e-cigarettes had a point-of-sale movable display<sup>43</sup>.

In 2013 Lorillard acquired the UK based e-cigarette maker Skycig<sup>52,53</sup> and in December 2012 BAT acquired the UK based start-up company CN Creative Limited specialised in the development of "next-generation products"; six months later CN Creative launched in the UK the e-cigarette "Vype"<sup>9</sup>.

According to news reports, the big tobacco companies invest huge sums into advertising for e-cigarettes<sup>10,42</sup>.

E-cigarettes are marketed to two consumer groups: smokers thinking about quitting and young social smokers or non-smokers<sup>23</sup>. E-cigarette ads focus mostly on harm reduction, use as a cessation aid, use as an alternative to cigarettes, being more environmentally friendly than cigarettes and sex appeal<sup>19,23,61,62</sup>.

Young people seem to be an important target group<sup>28</sup>: Internet ads are often placed on websites where a sizable percent of the audience are youth under 18 (up to 35 %) and young adults, 18–24 years of age (up to 34 %)<sup>62</sup>. For young people e-cigarettes are advertised as socially attractive trend<sup>23</sup>.

E-cigarette companies are present in social media as Facebook and Twitter as well as on YouTube - all are heavily used by youth. Most videos on YouTube on e-cigarettes are positive against e-cigarettes. Videos with positive content get more likes than those that criticize e-cigarettes<sup>54</sup>. In 2013 in London, Vype, owned by British American Tobacco, opened for two and half weeks the bar "#vypesocial". The events of this bar addressed young people<sup>51</sup>.

E-cigarette companies are also targeting stakeholder groups such as regulators, politicians and public health experts. To stakeholders e-cigarettes are promoted as harm reduction<sup>23</sup>.

In September 2013, in Great Britain one TV-spot and two radio ads have been banned<sup>2</sup>.

# 5 Users of Electronic Cigarettes

## 5.1 Socio-demographic characteristics

### ■ Evidence in 2013:

Electronic cigarettes are used primarily by smokers, smokers considering cessation as well as former smokers. Up to a quarter of smokers have tried electronic cigarettes at least once, but only between one and eight percent use them on long term.

Up to 13 percent of teenagers are at least occasionally users of e-cigarettes. Most adolescent users are smokers, but up to 4.7 percent are non-smokers.

### ■ New findings in 2013/2014:

#### Adults:

In 2012 and 2013 up to a third of smokers try e-cigarettes<sup>1,73,76</sup>, but still only a part of them, up to 19 percent, become regular users<sup>1,25,26,47,76</sup>. Most e-cigarette users are smokers<sup>1,26,76</sup>. Most consumers use the products occasionally; more ex-smokers than smokers use them daily<sup>26,76</sup>. Often, consumers use e-cigarettes and conventional cigarettes concomitantly (dual use), a much smaller proportion is exclusively e-cigarette user<sup>49</sup>.

#### Adolescents/young adults:

Up to 11 percent of adolescents and young adults (college students) have ever used e-cigarettes; prevalence is higher among older adolescents<sup>1,14,18,21,27,48,66</sup> and more boys than girls try e-cigarettes<sup>27,48,66</sup>; there is an upward trend in e-cigarette use among youth<sup>14,18,27</sup>.

As for adults, most adolescent e-cigarette users are smokers, but up to 20 percent are non-smokers<sup>1,14,18,21,27,48,66</sup>. Plenty more younger ever users are never smokers than older ever users<sup>18</sup>. Smoking

e-cigarette users smoke more conventional cigarettes than never and ex-users of e-cigarettes<sup>27</sup>. Some Adolescents appear to use e-cigarettes as cessation aid, as e-cigarette use is higher among youths who want or have tried to quit smoking<sup>48</sup>.

## 5.2 Reasons for using e-cigarettes

### ■ Evidence in 2013:

E-cigarettes are primarily used for two reasons: As smoking cessation aid and as an alternative to smoking.

### ■ New findings in 2013/2014:

13 percent up to half of the smokers use e-cigarettes as cessation aid<sup>1,47,58,73,76</sup>, 7 to 40 percent use them to cut down smoking, 4.5 percent use them, because they believe e-cigarettes have less adverse health effects than conventional cigarettes, and 5 to 28 percent use them to circumvent smoking bans<sup>1,73,47</sup>.

Smokers who are currently using e-cigarettes are more likely recently to have made a quit attempt than non-users<sup>76</sup>.

Preferred flavours of liquids are (in descending order): fruits, sweets, tobacco, drinks/beverages and mint. Most users (68 percent) daily switch between flavours and 73 percent like the variety of flavours<sup>34</sup>.

In 2010 a new tobacco control act was implemented in Poland, prohibiting smoking in public places and strengthening restrictions on promotion of tobacco products, but allowing marketing of e-cigarettes. The implementation of this law was associated with a temporary increase of internet searches for e-cigarettes and nicotine replacement therapy<sup>41</sup>.



## 5.4 E-cigarettes as potential initiation (“gateway”) product

### ■ Evidence in 2013:

Some young, non-smoking people might start using e-cigarettes, because they believe this to be less harmful than smoking cigarettes. Since most e-cigarettes contain nicotine, which is addictive, there is concern for young non-smokers who start using e-cigarettes developing nicotine dependence or, because of using e-cigarettes, becoming more familiar with smoking and eventually taking up cigarette smoking. Even though only a comparatively small

proportion of adolescent non-smokers takes up using e-cigarettes, this still means that a new market of nicotine use and dependence opens and develops – with unpredictable consequences.

### ■ New findings in 2013/2014:

According to a US survey including 2124 adults (>18 years) 44 percent of adults believe that e-cigarettes will encourage tobacco use among youth<sup>13</sup>.

E-cigarette use is increasing among youth and the percentage of never smokers among ever e-cigarette users is higher among younger adolescents than among older adolescents<sup>18</sup>.

## 6 Efficacy as Cessation Device

### 6.1 User opinions

#### ■ Evidence in 2013:

Many consumers believe that electronic cigarettes are helpful in an attempt to quit smoking: More than two thirds of users are using the devices to cut down or to mitigate withdrawal symptoms.

#### ■ New findings in 2013/2014:

Use of e-cigarettes as cessation aid is common among smokers calling Stop Smoking Services<sup>7</sup>.

Of 111 vapers, who had completely substituted smoking by e-cigarettes, 81 percent used liquids with nicotine contents above 15 mg/ml when they started vaping and initially often increased nicotine content. Those who initiated vaping with first generation devices reported that these devices were sufficient for reducing, but not for stopping smoking. After smoking cessation, vapers tended to reduce the nicotine content.<sup>35</sup>

### 6.2 Effects of electronic cigarettes on desire to smoke and withdrawal symptoms

#### ■ Evidence in 2013:

E-cigarettes – even products without nicotine – can reduce craving and withdrawal symptoms.

#### ■ New findings in 2013/2014:

In a small study including 16 smokers, first-time e-cigarette users judge – after one week e-cigarette use – e-cigarettes as less satisfying and enjoyable than conventional cigarettes, but they reduce craving nearly as successful as cigarettes<sup>74</sup>.

In 14 experienced vapers (6 smokers, 8 ex-smokers) the urge to smoke and withdrawal symptoms were reduced after

10 puffs within 5 minutes of a 18 mg/ml e-cigarette as well as after 60 minutes of ad libitum puffing<sup>22</sup>.

New-generation e-cigarettes reduce craving for cigarettes more effective than first-generation products<sup>36</sup>.

### 6.3 Efficacy of electronic cigarettes for sustained tobacco cessation

#### ■ Evidence in 2013:

Some smokers cut down smoking or quit completely as a result of using e-cigarettes, however, the efficacy of the devices as an aid for sustained smoking cessation has not yet been proven.

#### ■ New findings in 2013/2014:

Several new studies add to the growing evidence that some smokers cut down smoking while using e-cigarettes<sup>11,16,30,59,74</sup>, but total nicotine consumption seems to remain unchanged. Readiness to quit and confidence in quitting success may increase during e-cigarette use.<sup>74</sup>

A smaller proportion of smokers quit completely due to e-cigarette use. About a third of ex-smokers continues using e-cigarettes and some relapse to smoking.<sup>16,30,59</sup> E-cigarettes seem to have the same (weak) efficacy as cessation aid as nicotine patches.<sup>11</sup>

However, still the efficacy of e-cigarettes as an aid for sustained smoking cessation has not yet been proven<sup>4</sup>.

With regard to the use of e-cigarettes as cessation device it raises concern that in some liquids impurities are detectable above the level set for nicotine products in the European Pharmacopoeia<sup>31</sup>. Moreover, a considerable portion of ex-smokers that stopped with the aid of e-cigarettes continues using them on the long term, thus sustaining nicotine dependence<sup>16</sup>.

## 7 Product Regulation

### ■ Evidence in 2013:

Regulation of e-cigarettes varies strongly at international level. Several countries have banned manufacture, import and sale of e-cigarettes, other countries regulate production or sale or advertising, other have no regulation for e-cigarettes.

### ■ New findings in 2013/2014:

In February 2014 the European Parliament adopted a new directive concerning the manufacture, presentation and sale of tobacco and related products. According to this directive in the European Union all consumer electronic cigarettes will be regulated (except medicinal e-cigarettes or medical devices). The maximum level of nicotine will be 20 mg/ml, e-cigarettes may not exceed a volume of 2 ml and refill cartridges must not exceed a volume of 10 ml. Nicotine containing liquids must neither contain vitamins or additives that give an impression of health benefit, nor additives as caffeine or taurine that are associated with energy and vitality or additives with colouring properties for emissions. Only ingredients of high purity may be used in the nicotine-containing

liquid. Electronic cigarettes must deliver nicotine at consistent levels, the products have to be child- and tamper-proof and must be protected against leakage. Health warnings on e-cigarette packs will be mandatory, as will instructions for their use, information on addictiveness and toxicity, a list of all substances contained in the product and information on the product's nicotine content. Advertising for e-cigarettes will be banned. The new Directive should enter into force in May 2014. A transposition period of two years for Member States to bring national legislation into line with the revised Directive means that most of the new rules will apply in the first half of 2016.<sup>32</sup>

According to a 2013 US survey including 2124 adults (>18), there is high support for strong regulation: 88 percent want manufacturers to be required to test the products for safety, 86 percent want to prohibit the sale to minors (<18), 77 percent want e-cigarettes to be regulated like other nicotine products, 71 percent want to restrict marketing on social networking sites and 64 percent want to prohibit the use of e-cigarettes in indoor places and workplaces<sup>13</sup>.

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