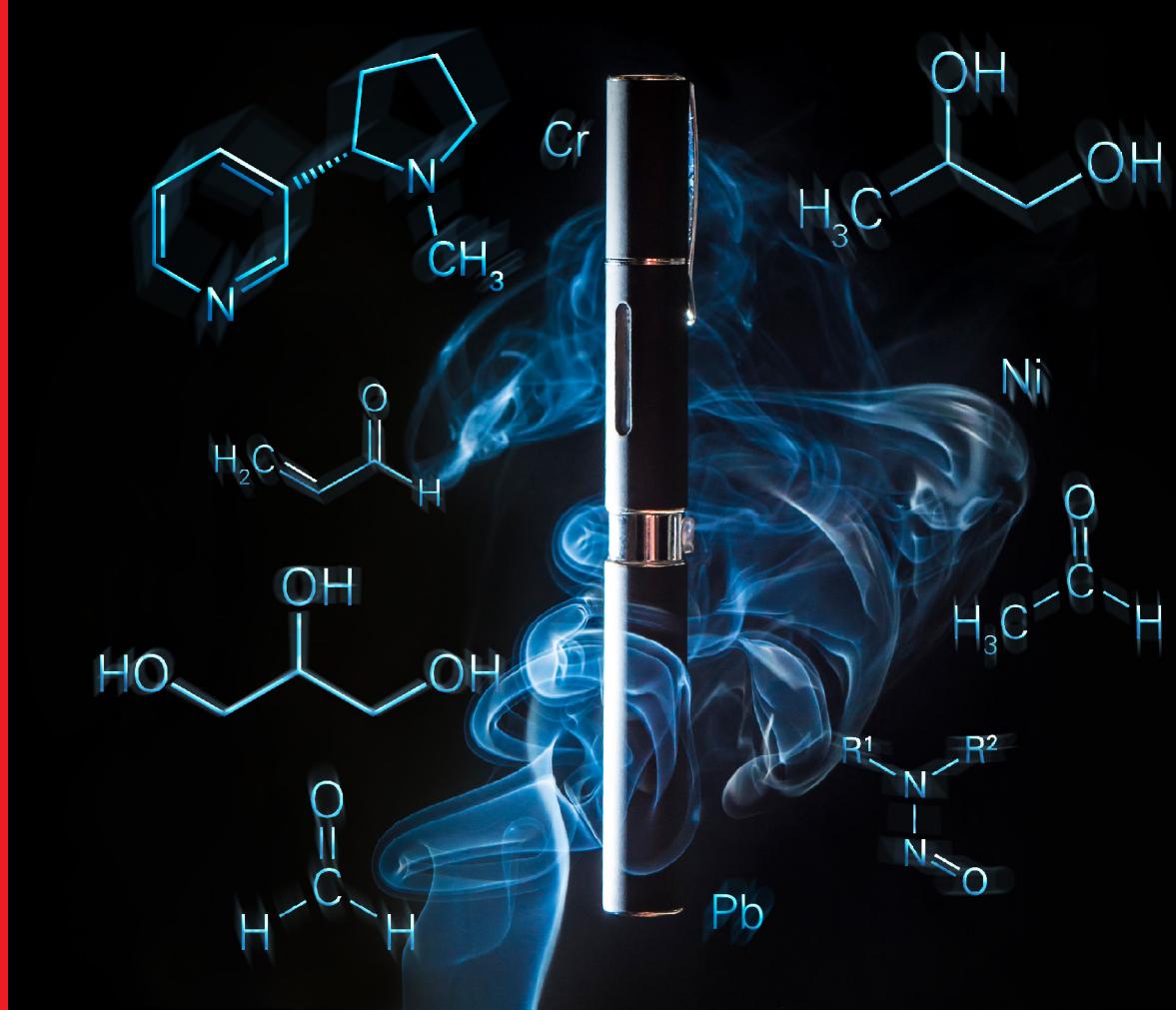




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Electronic Cigarettes – An Overview

**Red Series Tobacco Prevention and Tobacco Control Volume 19:
Electronic Cigarettes – An Overview**

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Red Series
Tobacco Prevention and Tobacco Control
Volume 19

Electronic Cigarettes – An Overview

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Preface

Protection of public health is an important task of governments. In the European Union, approximately 700 000 people die prematurely due to the consequences of smoking every year, making tobacco use the biggest preventable health risk. Therefore, it is an important task of politics to create an environment that prevents young people from taking up smoking and encourages smokers to quit. This process is also supported by regulatory measures.

The European Commission is currently revising the Directive on Tobacco Products (2001/37/EC). One of the changes planned is to include electronic cigarettes in the Tobacco Products Directive, because these products, which have been available in Europe since 2006, are regulated very inconsistently across member states.

There is a general consensus that electronic cigarettes need to be better regulated. Possible options for their regulation are: as medicinal products, medical devices, consumer products or tobacco products. In order to support the process of opinion formation on this issue, the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) has issued the present report, which evaluates currently available studies on product quality of electronic cigarettes, potential health implications and their usefulness as tobacco cessation aids.

The German Cancer Research Center welcomes the suggestion made by the European Commission to regulate electronic cigarettes as medicinal products. For one thing, regulation as medicinal products guarantees good product quality and for another, the products would thus be available for smokers who do not manage to quit by other means. Thus, electronic cigarettes are either used as an alternative to smoking to reduce tobacco use for harm reduction or as a new smoking cessation aid. Complete, sustained smoking cessation is a prerequisite for effective cancer prevention.

Prof. Dr. Dr. h.c. Otmar Wiestler
Chairman of the Management Board
and Scientific Director
German Cancer Research Center (DKFZ)
Heidelberg, April 2013

Key Messages

Electronic cigarettes are novel products emerging on the market just a couple of years ago. Consequently, there are only few scientific studies on the health implications of using electronic cigarettes.

Based on current data, the following statements can be made:

Product characteristics

- E-cigarettes cannot be rated as safe at the present time.
- Consumers do not have reliable information on product quality.
- Electronic cigarettes have various technical flaws (leaking cartridges, accidental intake of nicotine when replacing cartridges, possibility of unintended overdose).
- Some manufacturers provide insufficient and partly wrong information about their liquids.

Health effects

- The liquids contain ingredients that on short-term use irritate airways and may lead to allergic reactions and which may be harmful to health when inhaled repeatedly over a prolonged period of time.
- The aerosol of some liquids contains harmful substances (formaldehyde, acetaldehyde, acrolein, diethylene glycol, nickel, chromium, lead).
- The functionality of electronic cigarettes can vary considerably (aerosol production, nicotine delivery into aerosols).
- Adverse health effects for third parties exposed 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.

Users of electronic cigarettes

- Electronic cigarettes are used predominantly by smokers and smokers considering cessation as well as former smokers.
- Even though only few non-smokers use electronic cigarettes, the products may bring them closer to smoking conventional cigarettes.
- Electronic cigarettes are used as an alternative to cigarette smoking and as smoking cessation aids primarily because they are believed to be less harmful than regular cigarettes.

Efficacy as cessation device

- Electronic cigarettes – regardless of their nicotine content – can reduce the desire to smoke (craving) and withdrawal symptoms.
- Some smokers cut down smoking or quit smoking as a result of using e-cigarettes.
- The efficacy of e-cigarettes as an aid for sustained smoking cessation has not yet been proven.

Product regulation

- We desperately need to know more on product quality, ingredients, possible health effects of e-cigarette use, and efficacy of e-cigarettes as cessation aid. Carefully planned studies by qualified and objective scientists are necessary.
- Electronic cigarettes should be regulated as medicinal products, regardless of their nicotine content.
- E-cigarettes should not be dispensed to children and youth.
- Non-smoker protection legislation should apply to e-cigarettes.

1 Background

Electronic cigarettes (e-cigarettes) have been emerging increasingly on the tobacco market in recent years. E-cigarettes simulate smoking by technical means without burning tobacco. The devices consist of a power unit, an electric atomizer and a replaceable cartridge containing a liquid which is vaporized and inhaled when sucking at the mouthpiece. The main ingredients of the liquids are propylene glycol and/or glycerine, flavours (tobacco flavour, fruit flavours, chocolate, menthol, rum, coca cola, piña colada, ice cream, candy floss and many others) and, as a rule, nicotine; but there are also nicotine-free liquids. Electronic cigarettes are currently advertised as a possibility for nicotine consumption in smoke-free areas, as a less harmful alternative to smoking and, sometimes, as an aid for reducing smoking.

E-cigarettes are sold over the Internet, but they are also available in tobacco stores, pharmacies and supermarkets.

Based on current knowledge, electronic cigarettes cannot be regarded as safe, even though, unlike conventional cigarettes, they do not produce any combustion products. Only few studies are available to date on the effects of electronic cigarettes, their product safety and potential health consequences of their consumption, particularly in the long term.

Based on systematic literature research, the present volume gives a comprehensive overview of the prevalence of the products, the current state of knowledge about product characteristics and potential health risks of electronic cigarettes as well as their possible usefulness in tobacco cessation. It highlights the need for product regulation.

2 Product Characteristics

2.1 Large product variety

Electronic cigarettes vary widely in design, contents and operational features, however, most incorporate the general features as shown in Figure 2.1. When consumers draw on the mouthpiece or, in some models, operate a switch, the heating element is activated and vaporizes the liquid using heat at temperatures ranging from 65 °C to 120 °C. The smoker inhales the mist produced, which is visible as a fine vapour. Vapour is only produced while the heating element is activated, not in the breaks between puffs. In reusable products, the user replaces empty cartridges. Systems available include pre-filled replacement cartridges, open cartridges and dropper bottles with refill liquid. The product variety of electronic cigarettes is huge: There are re-usable e-cigarettes with disposable cartridges and those with refillable cartridges; disposable products designed for trying out and discarding when the liquid is used

up; individual parts and components for people who want to assemble their own electronic cigarettes. Some electronic cigarettes look like conventional cigarettes, while others are shaped like pens, pipes or others. They come in all shapes and colours and some are decorated with strass stones (Fig. 2.2).

Liquids for use in e-cigarettes are manifold, too. While flavouring mixtures initially all came from China, some vendors now claim that their liquids are made in Germany or other European countries, that they are manufactured in the pharmacy and fulfil quality standards^{107,108,112,125}. However, the exact origin of the ingredients is usually not clear. It is also not transparent what quality standards are being applied, and for which part or content of the product. Moreover, there is no guarantee that the ratio of ingredients used in the products is consistent: In some liquids tested, investigators found variations in the chemical composition of the same flavour in different bottles⁴.

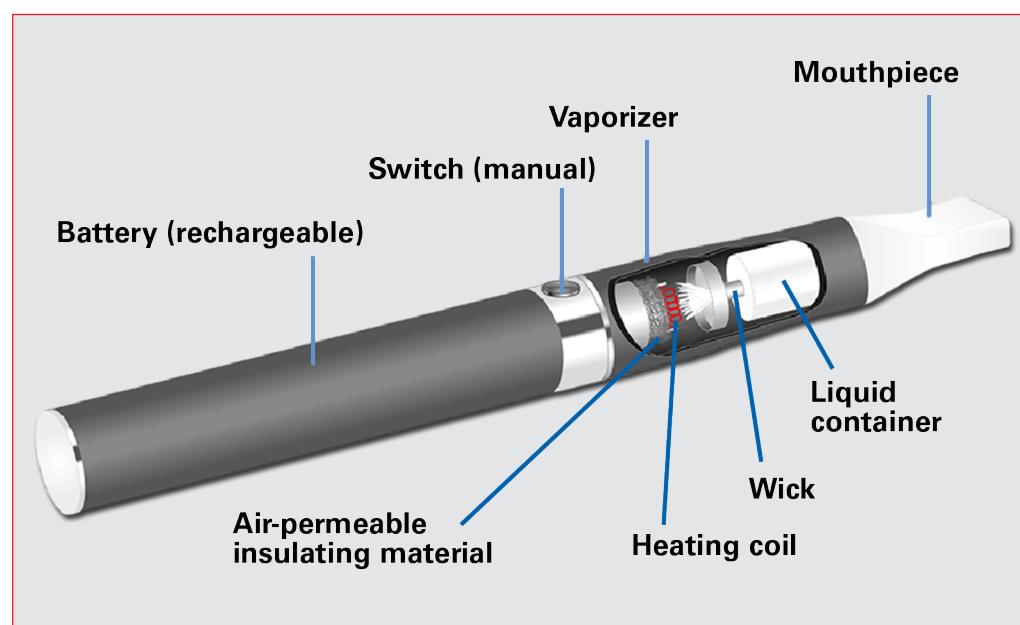


Figure 2.1
Components of electronic cigarettes.
Source: Fraunhofer WKI
(adapted)⁵²



Figure 2.2
Examples of different electronic cigarettes.

Source: Fraunhofer WKI⁵²

Furthermore, people can mix their own liquids. Instructions can be found, for example, on YouTube¹³⁴⁻¹³⁶. Online calculators are also available for creating your own ratio of ingredients¹³³. When creating their own mixtures, people can use not only substances contained in commercially available refill products, but also all kinds of other substances. For example, in one video a woman mixing her own liquid replaces water by vodka¹³⁵. Encouraging the manipulation of nicotine dosing properties and devising cocktails with alcohol and other drugs can be dangerous, and is contrary, for example, to the careful approach taken with respect to nicotine replacement dosages in which there are maximal standards for content, and recommendations for dosing to minimize risks.

The main ingredient of liquids for electronic cigarettes is propylene glycol, which is used for producing vapour. It can be replaced or supplemented by glycerine. Most E-liquids are also available with a large number of different flavours and flavours for some products include "tobacco extract" which may contain carcinogens and other toxic substances. Most liquids also contain nicotine. Consumers can usually choose from nicotine levels ranging from 0 to 18 milligrams per millilitre^{77,96,106}. Some manufacturers also offer higher nicotine levels of 20, 24 or 36 milligrams of nicotine per millilitre^{8,38,105}. Although the large product

variety makes it difficult to make an assessment, it is obvious that there are products with deficiencies in product safety and reliability and in the declaration of ingredients.

2.2 Technical problems and risk of overdose

Some e-cigarettes are of high quality design and manufacture, however, there are no government set standards for acceptable designs, contents and concentrations, purity, safety, and recommendations for safe use, and there is no convenient way for consumers to be able to access verified safety related data on individual products. Therefore, these products cannot be certified as "safe". For example, if smokers pull too hard on the device, liquid may enter the mouth⁹⁷ and nicotine contained in the liquid may be absorbed via the oral mucosa or involuntarily swallowed. Depending on the nicotine content, this may provoke symptoms of intoxication. When replacing or refilling cartridges, liquid may also ooze out and be spilled on your hands¹¹⁵. If liquids contain nicotine, it can be absorbed through the skin.

In addition, electronic cigarettes do not extinguish naturally after about ten puffs like conventional cigarettes, but can be used for hundreds of puffs without a break. When using them as intended, consumers may therefore get a

dangerous amount of nicotine by taking too many puffs, which may even result in serious symptoms of nicotine poisoning. According to the German Federal Institute for Risk Assessment and to press reports, there have already been cases of such poisoning^{12,73}.

In extreme cases, inferior products can be very dangerous. In the U.S.A., an electronic cigarette exploded during use for unknown reasons causing severe facial injuries to the consumer⁵⁰.

2.3 Variations in aerosol production and nicotine levels

The ingredients of the flavour solutions are vaporized. However, there is high variability between and within brands in the production of vapour. Different e-cigarette brands produce aerosols of varying density and aerosol density frequently declines during use^{116,128}.

Moreover, electronic cigarettes require sucking harder than conventional cigarettes¹¹⁶. In particular, intensity of drawing required to produce aerosol must be increased as the amount of liquid in the cartridge declines¹²⁸. As shown in an analysis of YouTube videos, users pull harder and significantly longer at most electronic cigarettes than at conventional cigarettes. Puff duration for e-cigarette users was a mean 4.3 seconds, as opposed to 2.4 seconds for tobacco cigarettes⁶⁶. Moreover, some e-cigarette users use stronger batteries to increase the amount of liquid vaporized by the device⁸⁶.

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 product characteristics as well as by user behaviour: A higher voltage power supply as well as longer puff duration markedly increase nicotine levels in vapour¹⁰³.

An analysis of 16 electronic cigarettes showed that 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 puffs⁵⁷. Efficacy of nicotine vaporization varies not only between brands but also within brands from one use to the next⁵⁷ (Fig. 2.3).

2.4 Deficiencies in declaration of liquid ingredients

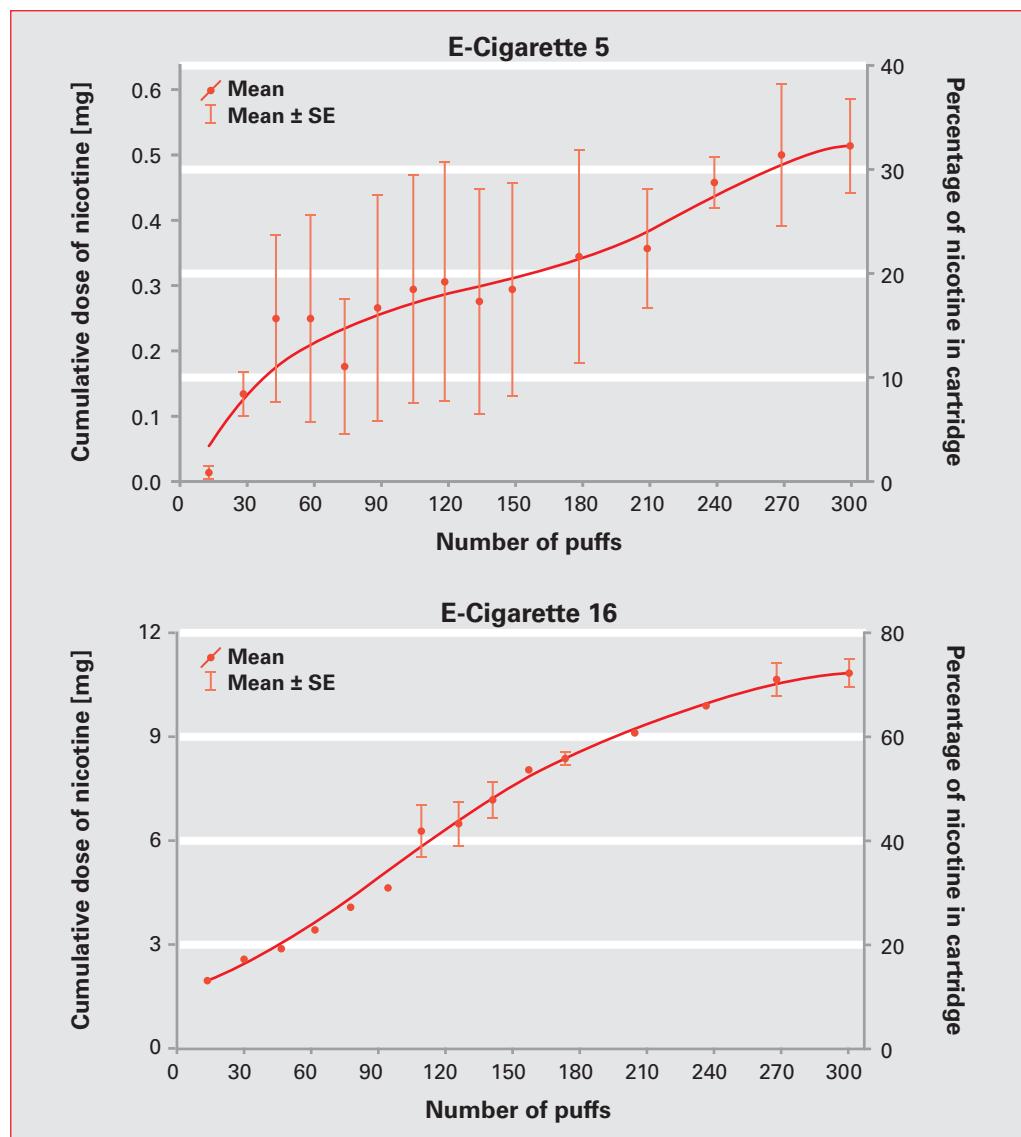
Declarations of nicotine levels contained in the liquids have been found to be incorrect – in several products grossly wrong^{16,18,57,61,114}. Small to significant amounts of nicotine were detected in solutions and refill cartridges declared as nicotine-free^{18,57,114}. Some products labelled as nicotine-free contained varying amounts of nicotine. In an extreme case, it was 21.8 milligram of nicotine per cartridge, which is roughly equal to a high nicotine dosage for liquids¹¹⁴. Conversely, a number of liquids labelled as nicotine-containing were found to contain significantly less nicotine than stated in the packaging information^{18,57,114}. An extreme example was a liquid labelled with 24 milligram nicotine per cartridge containing only 0.09 milligram of nicotine¹¹⁴. Other liquids labelled with 18 milligram nicotine per millilitre contained only two milligram of nicotine per millilitre⁵⁷. An analysis of 20 cartridges and 15 refill bottles showed that only in ten out of 35 samples the nicotine content was labelled correctly. Eighteen samples were found to have substantially less nicotine than declared and seven products contained between one and five milligrams of nicotine more than declared⁵⁷.

Consumers are left almost entirely in the dark about the nicotine content of cartridges labelled as “strong/high,” “regular/medium,” “light/low.” This labelling used by some manufacturers contains no information whatsoever about the actual amount of nicotine contained in these products.

On the Internet, consumers can also buy non-domestic liquids containing – apart from nicotine – other pharmacologically active substances such as tadalafil, used to treat Erectile Dysfunction, or the weight-loss agent rimonabant³⁷ which was taken from the market in the European Union in 2009⁶¹. According to a study by the U.S. Food and Drug Administration (FDA), some cartridges with these agents are incorrectly labelled. Fluids labelled as containing tadalafil were found to contain no tadalafil but an analogue, amino-tadalafil. In all products studied containing rimonabant, degradants of this substance were also detected⁶¹.

In conclusion it is clear that consumers cannot reliably identify the actual ingredients of a product. Due to flawed or wrong declaration, consumers may absorb nicotine unintentionally or at a higher dose than intended.

Figure 2.3
Delivery of nicotine into the vapour in different products. E-Cigarette 05 ("Trendy 808") vaporizes nicotine very ineffectively (delivers about 30 percent of nicotine from the cartridge into the vapour) and very inconsistently over 300 puffs (large standard deviation, mean SE); E-Cigarette 16 ("Gamucci 110228") vaporizes nicotine very effectively (about 70 percent of nicotine from the cartridge are delivered into the vapour) and very consistently over 300 puffs (low standard deviation, mean SE).
Source: Goniewicz et al. 2013⁵⁷
Illustration German Cancer Research Center 2013



Conclusion

Existing product flaws require regulation obliging manufacturers and vendors to provide the following information:

- Exact declaration of ingredients of liquids on the packaging (purity, impurities, stability).
- Estimate of exposure to ingredients when using electronic cigarettes for short-term and long-term use.

- Toxicological evaluation of inhaled intake of all ingredients for short-term and long-term use.
- Assessment of health risks associated with short-term and long-term use of electronic cigarettes.
- Assessment of addictive potential of nicotine-containing products.
- Assessment of exposure of third parties (second-hand smoke).

3 Health Effects

3.1 Potential health risks from ingredients

Health risks associated with intended use of electronic cigarettes cannot be excluded at present. Generally, nicotine-containing liquids are potentially dangerous, because nicotine is toxic and addictive. However, not even nicotine-free liquids are necessarily harmless. Their main ingredients (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. There are currently no studies available on the effects of long-term use of e-cigarettes.

In the following, potential health risks of the individual ingredients of e-liquids are outlined.

3.1.1 Propylene glycol

Propylene glycol is the main ingredient of e-liquids and is used in e-cigarettes for producing vapour. In the European Union, propylene glycol is an approved food additive (functioning as a humectant and solvent for colours and flavours)^{2,43}. But it is also frequently used as a humectant in cosmetics and medical products to be applied to the skin and also as an industrial antifreeze and deicing agent for cars, airplanes and boats².

Safety data sheets for industrial use of propylene glycol caution that the substance may form explosive gas/air mixtures and that heating or burning may lead to toxic gases being formed. Measures recommended in case of unintended release include ample ventilation and avoiding inhalation. The U.S. Food and Drug Administration (FDA) has classified propylene glycol as “generally recognized as safe” (GRAS) for oral

intake (swallowing)¹³. However, completely different values may apply for intake through the lungs (inhalation), because the lungs have a very large exposed surface area.

To date, only few studies have been conducted on potential health risks associated with inhaling propylene glycol – as one does when using electronic cigarettes as intended. According to these studies, inhaling propylene glycol may affect airways. Short-term exposure to propylene glycol in indoor air (309 mg/m³ for one minute) already causes irritations in the eyes, throat and airways¹²⁷. Long-term exposure to propylene glycol in indoor air may raise children’s risk of developing asthma²⁰. People who have frequently been exposed to theatrical fogs containing propylene glycol are more likely to suffer from respiratory, throat and nose irritations than do unexposed people⁸⁸. We may therefore assume that the use of e-cigarettes, which involves inhaling propylene glycol vapours several times daily, may cause respiratory irritations. This applies, in particular, to individuals with impaired airways and to smokers who switch to e-cigarettes or use them additionally, because smokers usually already have impaired airways. Some e-cigarettes manufacturers caution accordingly: “Use the product with utmost caution if you are suffering from a disease of the lungs (e.g. asthma, COPD, bronchitis, pneumonia). If your lungs are impaired, the vapour released may cause asthma attacks, dyspnoea, and coughing fits. Do not use the product if you experience any of these symptoms!”⁹⁵.

3.1.2 Glycerine

Alongside propylene glycol, electronic cigarettes frequently also contain glycerine for aerosol production. Glycerine is considered generally safe for oral intake

and is used in food production as a humectant and as a solution carrier in flavours. However, this does not necessarily mean that it is also safe for inhalation – as in e-cigarettes if used as intended. These concerns are not unfounded. The specialist journal *Chest* reports about a case study of a patient with lipid pneumonia caused by glycerine-based oils from the aerosol of electronic cigarettes. The link appears to be clear, since symptoms disappeared when the patient stopped using electronic cigarettes⁸⁴.

3.1.3 Nicotine

Nicotine has many effects on the body^{6,70,117} (Fig. 3.1): It raises blood pressure and heart rate, curbs appetite, increases basal metabolic rate and activates bowel movements, which may lead to diarrhea. In addition, it lowers urine production, promotes blood coagulation, stimulates breathing, increases pain

sensitivity and may cause nausea and vomiting. In the brain, nicotine promotes release of several neurotransmitters causing various psychological effects, which may lead to dependence.

Nicotine unfolds at least part of these effects also when using electronic cigarettes. Use of nicotine-containing e-cigarettes raises the heart rate: When using an e-cigarette with at least ten milligram per millilitre of nicotine, pulse was found to increase within the first five minutes from 73.2 to 78 beats per minute. These values were measured in individuals who have used e-cigarettes for at least three months and hence are experienced product users¹²².

Large amounts of nicotine are toxic: Approximately 50 milligram of nicotine are lethal if swallowed⁸⁰; for children, a dose of only six milligrams is already life-threatening¹³. Liquids used in e-cigarettes usually contain between 6 and 26 milligram per millilitre or even up to

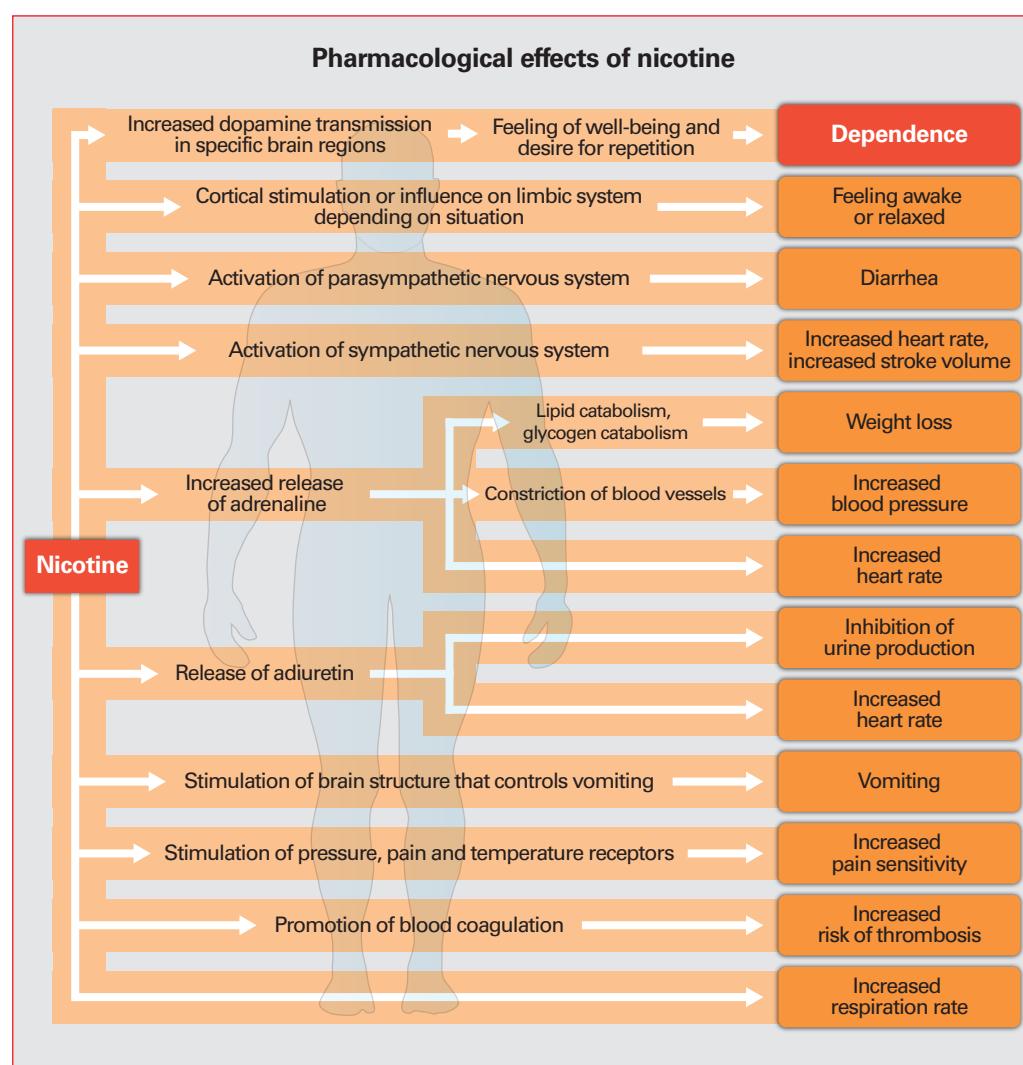


Figure 3.1
Pharmacological effects of nicotine.

Source: German Cancer Research Center 2008³²
Illustration: German Cancer Research Center
2013

36 milligram per millilitre of nicotine. Cartridges, particularly those containing up to 50 millilitres, therefore pose a serious threat to children if they swallow the content due to carelessness¹⁶.

Nicotine crosses the placenta and is absorbed by the fetus; it can damage the fetal lungs, heart, and the central nervous system⁸¹. Therefore pregnant women should abstain from e-cigarette use.

Some e-cigarette vendors caution about health risks associated with nicotine. However, even more problematic than the toxic effects of nicotine, which are to be expected primarily due to overdose, are its pharmacological effects on the brain. The substance binds to nicotine receptors in the brain leading to release of various messenger substances stimulating the reward centre, thereby provoking a feeling of well-being⁷. Over time, this can lead to craving for nicotine and, ultimately, to nicotine dependence. This dependence consists of a physical and a psychological component, making cessation particularly hard⁷.

When using nicotine-containing electronic cigarettes, nicotine levels in the blood increase, even though the devices seem to deliver nicotine to the body more slowly and at lower levels than conventional cigarettes. While smoking makes blood nicotine levels rise to a maximum of approximately 15 to 20 nanograms per millilitre after an average of 14.3 minutes, using e-cigarettes raises blood nicotine levels to no more than 3.5 nanograms per millilitre after 19.6 minutes^{10,39,121}. These measurements were taken in first-time users of electronic cigarettes. Nicotine levels in study participants who had used e-cigarettes for several months increased to between 10 and 15 nanograms per millilitre¹²². It is possible that participants who were more experienced in using the products pulled harder at the devices leading to increased nicotine delivery.

Since users of electronic cigarettes absorb nicotine when vaping, it is possible that smokers who have switched to e-cigarettes or are using them in addition to conventional cigarettes may maintain nicotine dependence¹³⁰ because of the smoking ritual being maintained. Currently, e-cigarettes are primarily used by smokers and former smokers^{41,42,51,63,72,85,90,98}, but the large variety of flavours, amongst other, makes the products particularly appealing to young people and possibly even to

non-smokers¹³⁰. However, it is particularly important to protect young people from any kind of dependence.

3.1.4 Cancer-causing substances (carcinogens)

Individual liquids were found to contain small amounts of nitrosamines^{55,76,114,126}. In addition, formaldehyde, acetaldehyde and acrolein were measured in the aerosol of various e-cigarettes, although considerably less than in cigarette smoke^{55,76,110,119} (Fig. 3.2). Formaldehyde and acrolein were only found in glycerine-containing liquids; they probably form upon heating of glycerine^{55,110}. Acrolein is absorbed by the user: A decomposition product of acrolein was detected in the urine of e-cigarettes users, although considerably less than after smoking conventional cigarettes⁵⁶. In addition, nickel and chromium were detected in the aerosol, with higher levels of nickel measured than it is known to be present in cigarette smoke¹²⁹.

The aforementioned substances have been classified by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) and the International Agency for Research on Cancer (IARC) as carcinogenic^{30,69}. Since there is no safe threshold value for these substances, it cannot be excluded that using electronic cigarettes increases cancer risk, even though these substances may be present in very small amounts.

3.2 Side effects

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^{17,26,41,93}.

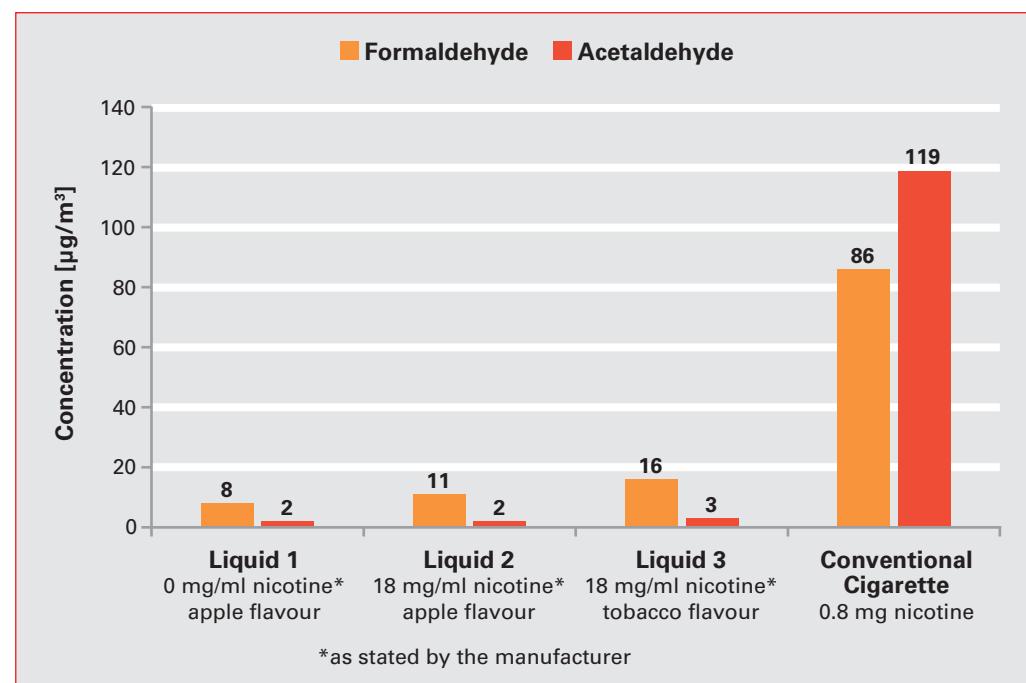
Data on the impact of e-cigarette use on pulmonary function are not conclusive. A study involving 30 participants reports adverse effects on pulmonary function after using an electronic cigarette for five minutes; however, the long-term pulmonary effects of e-cigarette use are unknown at the present time¹²⁴. Another study did not find any effects of e-cigarette use or second-hand use (comparable to second-hand smoking) of e-cigarettes on pulmonary function⁴⁸.

Since 2008, the U.S. Food and Drug Administration (FDA) has received 47 reports about side effects of electronic cigarettes.

Figure 3.2
Concentrations ($\mu\text{g}/\text{m}^3$) of formaldehyde and acetaldehyde in indoor air after using an e-cigarette filled with different liquids and a conventional cigarette.

Source: Schripp et al. 2013¹⁰²

Illustration: German Cancer Research Center 2013



These included eight reports about severe adverse events (such as pneumonia, congestive heart failure, burns due to explosion of the product, possible infant death secondary to choking on an e-cigarette cartridge). Although there is not necessarily a causal relationship between e-cigarette use and the reported symptoms¹⁹, health concerns about electronic cigarettes are definitely justified.

An alarming finding was the detection of diethylene glycol in the liquid of one product¹²⁶. This substance may lead to serious adverse health effects and even to death if swallowed¹⁰¹. It may be harmful if liquid gets into the mouth due to technical flaws when puffing at the electronic cigarette. It is unknown whether the substance is dangerous on inhalation.

Potential health consequences of long-term use of e-cigarettes have not yet been studied, because the products started being marketed only a few years ago.

3.3 Improvement of acute tobacco-related health problems

Health improvements (fewer sore throats, improved breathing and body fitness) reported by many users after switching to electronic cigarettes^{41,63} 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 following smoking cessation after starting consumption of electronic cigarettes⁴⁷. This observation is supported by a study with 15 electronic cigarette users, that reported no impact of e-cigarette use on white blood cells⁴⁹.

3.4 Indoor air pollution

E-cigarettes are not emission-free. When using electronic cigarettes, volatile organic substances including propylene glycol, flavours and nicotine as well as liquid particles of less than 2.5 micrometre ($\text{PM}_{2.5}$) diameter are emitted into indoor air^{83,91,102}. These ultrafine liquid particles may penetrate deeply into the lungs. However, electronic cigarettes produce substantially fewer ultrafine particles than conventional cigarettes^{83,91} (Fig. 3.3).

Substances emitted into indoor air when electronic cigarette are used may be inhaled by non-users present in the same room. Therefore, adverse health effects for third parties due to second-hand exposure can not be excluded.

To date, few studies have been conducted on the substances in the mist of e-cigarettes. According to these studies, the aerosol of the products studied contains, besides large amounts

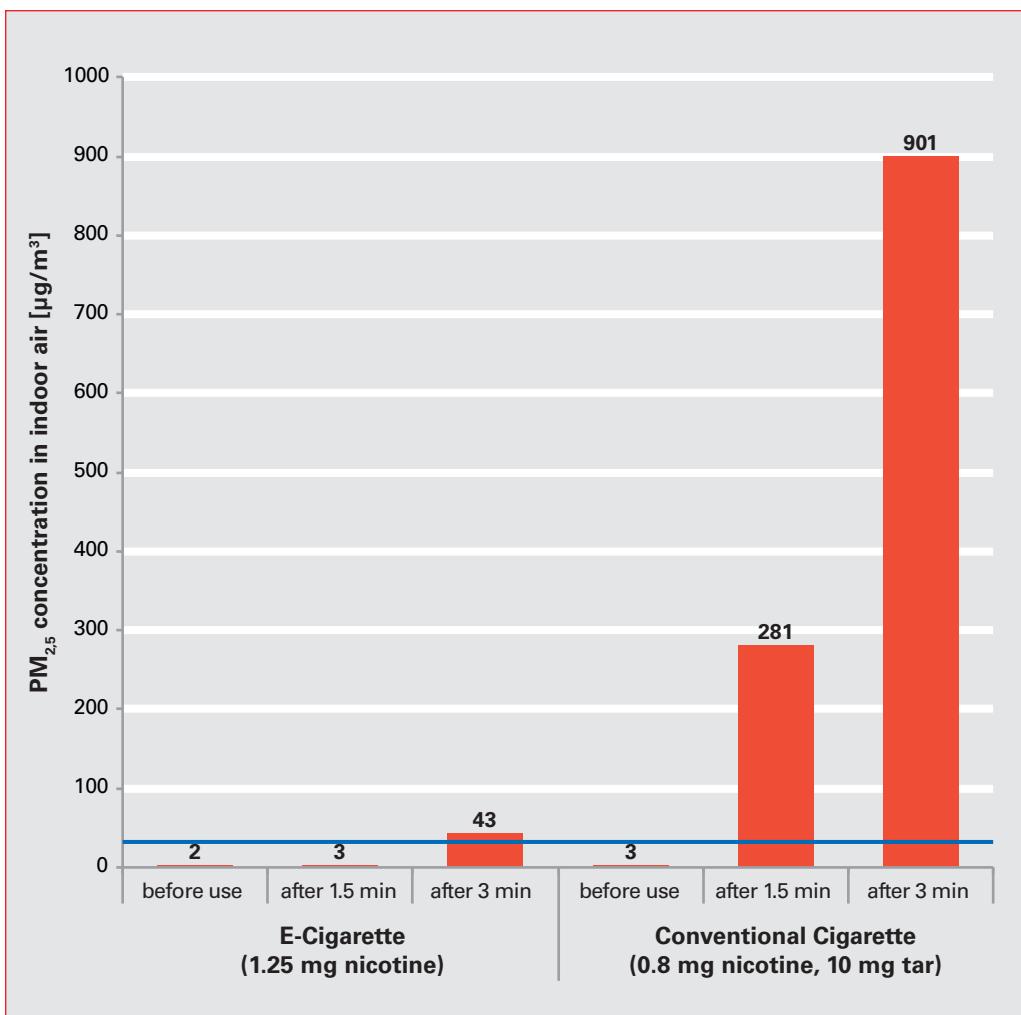


Figure 3.3
Concentration of PM_{2.5} (µg/m³) in indoor air before and after of using an e-cigarette and a conventional cigarette.
Blue line: WHO air quality guideline value for PM_{2.5} for short term exposure (24 hour mean).

Source: Pellegrino et al.

2012⁹¹

Illustration: German Cancer Research Center 2013

of propylene glycol, the main ingredient of the liquids, also nicotine^{24,83,91}, flavours⁹¹, tobacco-specific nitrosamines, volatile organic compounds, acetone, formaldehyde, acetaldehyde, benzo(a)pyrene and PM_{2.5}^{83,102} as well as silicate and various metal particles¹²⁹. Particle size in aerosol is between 100 and 600 nanometres and hence comparable to that of particles found in tobacco smoke of conventional cigarettes¹³⁷. Although levels of most substances measured are lower in the mist of electronic cigarettes than in conventional cigarette smoke, they do pollute indoor air²⁴. Four of the metals measured (sodium, iron, aluminium and nickel) are present at higher levels than those known in cigarette smoke; five others (copper, magnesium, lead, chromium, manganese) are present in the same amounts; and two (potassium, zinc) at lower levels¹²⁹. Nickel and chromium are carcinogenic, lead is suspected to be carcinogenic^{30,69}. 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.

Conclusion

According to currently available data, the electronic cigarette is no safe product:

- Propylene glycol may cause respiratory irritations and possibly increase the risk for asthma.
- Nicotine is addictive. Refill cartridges with high nicotine contents are potentially life-threatening, particularly for children.
- Carcinogenic substances are found in some aerosols.
- Using e-cigarettes leads to emission of propylene glycol, ultrafine liquid particles, nicotine and carcinogenic substances into indoor air.
- We desperately need to know more on the possible health effects of e-cigarette use. Carefully planned studies by qualified and objective scientists are necessary.

4 Product Awareness and Market Development

Awareness of the electronic cigarette in the population is high, particularly among smokers, although it continues to be a niche product that is not very widespread. However, sales have grown considerably over recent years.

According to a survey conducted on behalf of the European Commission (Special Eurobarometer 385) in 2012, two thirds (69 percent) of Europeans had heard of electronic cigarettes. 46 percent also know what they are, while 23 percent are not really sure. Men and younger people (15-39 years old) are more likely to be aware of the products than are women and older people (over 55 years old). Highest awareness of the product is found in Finland (92 percent), Greece (90 percent), and Lithuania (88 percent). Most Germans (80 percent) have heard of the products and 57 percent also know what they are. Awareness of the devices is lowest among people in Sweden (34 percent) and Ireland (47 percent)¹¹³.

According to various international studies, between 60 and over 80 percent of smokers are aware of electronic cigarettes^{22,71,89}. At approximately one third, awareness is lower among non-smokers²². According to a representative study (International Tobacco Control – ITC – Four-Country Survey) conducted from July 2010 to June 2011 in the U.S., Canada, Australia and the United Kingdom involving smokers and non-smokers, almost half of respondents (46.6 percent) had heard of electronic cigarettes. Awareness was significantly lower in those countries where electronic cigarettes are illegal (Canada: 39.5 percent, Australia: 20 percent) than in those countries where they are legal (U.S.: 73.4 percent, U.K.: 54.4 percent)¹. According to surveys conducted by the Society for Consumer Research (GfK) in Germany, awareness of electronic cigarettes among smokers in Germany has increased: In 2012,

78.3 percent of smokers were aware of the products; in 2013, 81.2 percent of smokers were aware of them^{53,54}.

Awareness of e-cigarettes is also high among young people. In Poland, 86.4 percent of a total of 13,250 pupils and students between the ages of 15 and 24 years had heard of the products⁵⁹, and in a survey conducted in the U.S. with 228 male adolescents aged 11 to 19 years, 67 percent of participants (91 percent non-smokers, 9 percent smokers) were aware of electronic cigarettes. 74 percent of smokers and 13 percent of non-smokers were willing to try them⁹².

The Internet seems to play a substantial role for product awareness of electronic cigarettes. In an online survey with 1,347 participating e-cigarette users from 33 countries (72 percent European), 41 percent of participants said they knew e-cigarettes from the Internet. 35 percent of participants had first heard of the product from a friend and eight percent saw another person use an e-cigarette²⁶.

Increased marketing of electronic cigarettes presumably also contributes to rising product awareness. In the U.S., e-cigarettes not only have been marketed over the Internet but have also been promoted in entertainment shows. In 2010, electronic cigarettes were distributed as free give-aways to guests at the Grammy Awards. They are also increasingly used in Hollywood movies⁶⁰. In Germany, in December 2011 advertising spots on e-cigarettes have been broadcasted on TV (Fig. 4.1).

An analysis of Internet search queries in the United Kingdom, Australia, Canada and the United States has shown that interest in electronic cigarettes has been increasing continuously since 2008³. In the U.S., sales of e-cigarette kits grew nine-fold and sales of refill cartridges grew more than fourteen-fold from 2010



Figure 4.1
Advertising spots on German TV.
Photos: German Cancer Research Center 2011

to 2012⁶⁷ (Fig. 4.2). The number of e-cigarette users in the U.S. increased by four times from 2009 to 2010⁹⁸.

Electronic cigarettes were introduced to the European market in 2006 and accounted for only 0.4 percent of the total tobacco product market in 2010 – equalling nicotine replacement products. According to estimates of electronic cigarette vendors, there were between 200,000 and 400,000 users in the U.K. and 1.2 million in Germany in 2011⁸².

It is difficult to assess market development in Europe, where e-cigarette trade is highly fragmented. The market is made up predominantly of vendors and there are hardly any manufacturers; it is dominated by small companies with less than 10 up to a maximum of 30 employees⁸². According to data collected by the U.K. Electronic Cigarette Consumer Association, the number of e-cigarette consumers has increased from a few hundred in 2006 to approximately 600,000 in 2012 and the e-cigarette market has grown by an average of 500 percent annually; in 2012, the annual market growth rate was estimated to be around 50 percent⁴⁰. In Germany, the market for e-cigarettes grew rapidly in 2011⁸².

Some vendors in Germany rate e-cigarettes as a promising product. Tobacco retailers in Germany reported in 2011 that e-cigarettes sold extremely well, particularly in the Christmas season (see quotations in the box below). But they also said it was unclear whether this trend would continue³⁴. The legal situation in Germany is unclear at present – electronic cigarettes are neither explicitly illegal nor explicitly legal in Germany – and there is a possibility that sale of these products

through retailers may be prohibited. Therefore, it is not possible to give a prospect of how the market for electronic cigarettes will develop in Germany.

The tobacco industry seems to expect that popularity of e-cigarettes and other products associated with fewer health risks than cigarettes will continue to increase, as tobacco manufacturers have started incorporating electronic cigarettes into their product portfolios. In 2012,

"The good thing about e-cigarettes is that they bring additional sales to our business without resulting in any drops in tobacco sales."

Tobacco retailer Kay Habersaat from Hamburg (Tabakland), Die Tabak Zeitung of 13 January 2012³⁶

"There were some months when we made more profit than with tobacco products. This has started stagnating somewhat, but it still shows promise."

Tobacco retailer Oliver Harmsen (Tabak Box, Hannover), Die Tabak Zeitung of 13 January 2012³⁶

"The electronic cigarette was the top seller of the year-end business. The demand boom peaked in the Christmas season. [...] The e-cigarette was totally in vogue. As a retailer, you simply cannot resist such a strong demand."

Steffen Brinkmann, tobacco retailer in Schwerin and Wismar, Die Tabak Zeitung of 6 January 2012³⁵

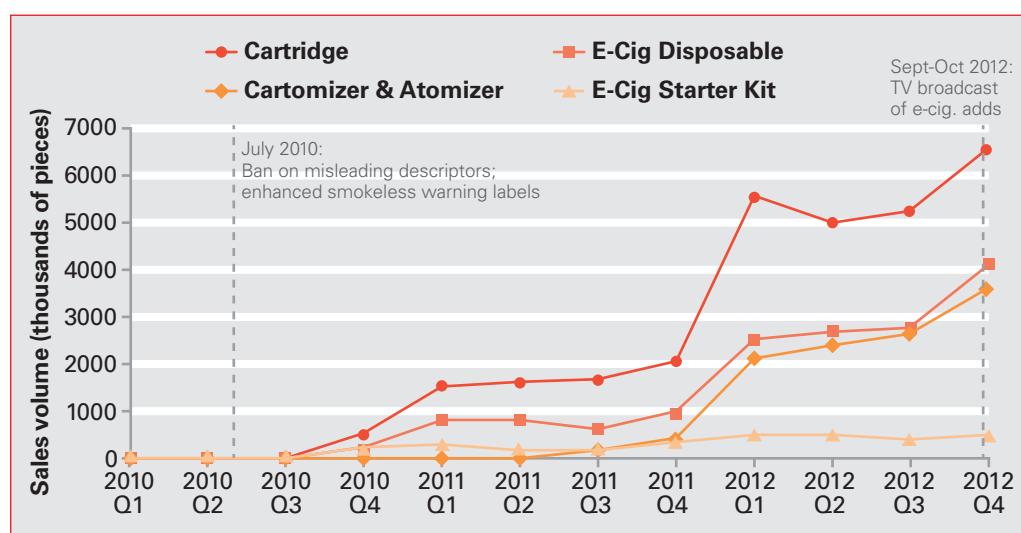


Figure 4.2
Analysis of e-cigarette sales figures in the U.S. based on product barcodes.

Source: Huang et al. 2013⁶⁸

Illustration: German Cancer Research Center 2013

U.S. cigarette manufacturer Lorillard acquired a leading e-cigarette company in the U.S. ("blu eCigs"). Electronic cigarettes have emerged as a successful growth area with good income results for the company already in the first year^{78,79}. A subsidiary of U.S. tobacco giant Reynolds American Inc., Reynolds Vapor Company, started testing an electronic cigarette with the brand name "Vuse" in a limited market in 2012⁹⁹. British American Tobacco established a stand-alone start-up company, Nicoventures Limited, focusing on the commercialisation of new products with reduced health risks⁹. Philip Morris are currently developing their own electronic cigarettes. They are developing tobacco cigarettes which are heated electronically and electronic

cigarettes which vaporize fluids. The company plans to conduct quality controls and clinical trials to study health risks and plans to launch the first products on the market by 2017¹⁵.

Conclusion

- 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.
- E-cigarettes have a very small share of the total tobacco market.
- Only few people are employed in the e-cigarette trade.
- Sales have grown strongly over recent years.

5 Users of Electronic Cigarettes

5.1 Socio-demographic characteristics

Globally, electronic cigarettes (e-cigarettes) are apparently used primarily by smokers, smokers considering cessation as well as former smokers^{1,22,41,85,90,98}. 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.

According to a nationally representative cross-sectional survey from the U.S.A. conducted in 2011, about 20 percent of smokers had tried e-cigarettes and eight percent had used them within the last month prior to the survey⁹⁴. Smokers intending to quit were more interested in e-cigarettes than were smokers with no intentions to quit. In addition, slightly more women than men tried electronic cigarettes. Within the last month preceding the survey, smokers with a lower educational degree or with lower incomes were more likely to use e-cigarettes than smokers with a higher educational degree or a higher income⁹⁴.

By contrast, an analysis of data from the International Tobacco Control Four-Country Survey found that only 7.6 percent of all respondents (smokers from the U.S., the United Kingdom, Australia and Canada) had ever tried electronic cigarettes and 2.9 percent were current users at the time of the survey. In all countries studied, younger respondents with higher education and higher incomes tended to be more aware of e-cigarettes than other socio-demographic groups. Among those who were aware of e-cigarettes, younger female smokers, current smokers and daily smokers were more likely to actually try e-cigarettes than were former smokers¹.

In further surveys conducted in 2010 and 2011 in the U.S., between six and seven percent of participants (smokers

and non-smokers) had tried electronic cigarettes at least once^{22,71} and 1.2 percent had used them within the last 30 days prior to the survey²². Smokers were more likely to try e-cigarettes: 28.5 percent of smokers had ever used the devices, compared to only 2.7 percent of non-smokers²².

In a survey from the Czech Republic, about a quarter of 837 surveyed smokers reported to have ever tried e-cigarettes and 27 percent of those who had ever tried these products were regular users⁷². According to Eurobarometer (Special Eurobarometer 385), a total of seven percent of respondents from the 27 EU countries have ever used e-cigarettes: five percent have tried them once or twice and only one percent each are occasional or regular users; the same holds true for Germany¹¹³. Across Europe, prevalence of trying electronic cigarettes is highest in Bulgaria and Lithuania (11 and 10 percent of respondents, respectively). A maximum of three percent of respondents in each European country were permanent users of e-cigarettes.

In Germany, surveys conducted by the Society for Consumer Research (GfK) show that trying or regular use of electronic cigarettes is restricted almost entirely to smokers^{53,54}. In 2013, 81.2 percent of surveyed smokers had heard about electronic cigarettes but had not tried them; 13.7 percent had tried them but were not using them any longer, and 0.7 percent of smokers were current users at the time of the survey^{53,54}. In 2012, it was mainly people aged between 20 and 29 years who tried these products, whereas in 2013 more triers were found in the age group ranging from 20 to 59 years. A survey conducted in Munich involving 320 smokers showed that men and people with a rather mild addictiveness to nicotine are more likely to use electronic cigarettes. E-cigarette users showed higher motivation to quit smoking than cigarette smokers¹⁰⁰.

An online survey to which e-cigarette users from 33 countries responded – 72 percent of these were European countries – revealed only minor gender-specific differences in the use of e-cigarettes: Men tended to prefer liquids with tobacco flavour, while women tended to prefer chocolate flavour or some other sweet flavour. As to the preferred nicotine content of the liquids, the survey did not reveal any gender-related differences. Significantly more women than men agreed with statements saying that they liked the taste of e-cigarettes; that they liked e-cigarettes because they are similar to normal cigarettes; and that they can ease the craving for nicotine²⁶. The relatively high proportion of adolescents and young adults who try electronic cigarettes is alarming. Of a total of 13,250 pupils and students between the ages of 15 and 24 years in Poland, about 20 percent had ever tried the devices and almost seven percent had used them during the month prior to the survey. Boys (26.9 percent) were more likely to try the products than girls (13.9 percent) and significantly more smokers (11.3 percent) were using them than were non-smokers (0.8 percent)⁵⁹. According to the Global Youth Tobacco Survey (GYTS), in 2012 in Hungary 13 percent of teenagers aged 13 to 15 years had used electronic cigarettes within the last 30 days prior to the survey (16 percent of boys and 11 percent of girls), with most of them (93.3 percent) also being occasional or daily smokers²⁷. Use of e-cigarettes was higher among nondaily smokers (60.7 percent) than among daily smokers (31.5 percent). Among those adolescents who were non-smokers, 4.7 percent were users of electronic cigarettes¹³². According to GYTS, in Lithuania 9.1 percent of teenagers aged 13 to 15 years were users of e-cigarettes (10.3 percent of boys and 7.7 percent of girls))¹³¹.

5.2 Reasons for using e-cigarettes

Electronic cigarettes are primarily used for two reasons: As an alternative to smoking and as a smoking cessation aid. According to the ITC Four-Country Survey, almost 80 percent of respondents used e-cigarettes to reduce the health risks of tobacco smoking and three quarters of respondents stated using them to help

them quit smoking¹. In an international survey conducted on the Internet with participants from 33 countries, 76 percent of participants stated using electronic cigarettes as an equal alternative to smoking. Further reasons reported included: the desire to quit smoking (7 percent), health reasons (6 percent), costs (3 percent) and avoiding smoking bans (3 percent)²⁶.

In another Internet survey conducted in Poland with 179 participating e-cigarette users, 41 percent of participants stated that they used electronic cigarettes because they are considered to be less harmful, and just as many used them to help them quit smoking⁵⁸.

5.3 Assessment of health risks associated with e-cigarettes

According to Eurobarometer, people in the European Union consider electronic cigarettes to be comparatively harmless: Not even a third (27 percent) of Europeans consider electronic cigarettes to be harmful; over a third (35 percent) perceive them as harmless and another third do not have any opinion about this issue. In particular, young people under the age of 25 (45 percent), university students (43 percent), and smokers (43 percent) tend to perceive electronic cigarettes as not harmful¹¹³.

The vast majority (82 percent) of participants in the web-based survey conducted in Poland believed that although electronic cigarettes are not completely safe, they are less dangerous than conventional cigarettes. 60 percent believed that electronic cigarettes are less addictive than conventional cigarettes⁵⁸. In the ITC Four-Country Survey, the vast majority (70.3 percent) of surveyed smokers who were aware of e-cigarettes believed them to be less harmful than traditional cigarettes (63.9 percent in Canada, 65.9 percent in the U.S., 82.2 percent in the U.K. and 71.0 percent in Australia)¹.

5.4 E-cigarettes as a potential initiation ("gateway") product

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 smoking⁶⁴. First Studies indicate that this concern is not unfounded.

Participants of a survey from the U.S. involving a total of 66 young adults (18-26 years old) who took part in focus group discussions about novel tobacco products including electronic cigarettes stated that electronic cigarettes take users one step closer to smoking so that they would eventually take up cigarette smoking. Half of the participants, whether they were smokers or non-smokers, admitted they would try an electronic cigarette if offered by a friend²¹.

According to an Internet survey conducted in Poland, 64 percent of participants were cigarette smokers when they started using e-cigarettes and had quit smoking regular cigarettes at the time of the survey. But 25 of a total of 179 participants (14 percent) were non-smokers when they started using e-cigarettes. Of these, 20 percent reported that they had also started cigarette smoking through the use of electronic cigarettes⁵⁸.

In the Global Youth Tobacco Survey conducted in 2012 in Hungary among teenagers aged between 13 and 15 years,

6.7 percent of participants who had used e-cigarettes within the last 30 days prior to the survey were non-smokers²⁷ and 4.7 percent of participants who had never smoked before had used e-cigarettes within the last 30 days prior to the survey¹³². Although willingness to try electronic cigarettes seems to be particularly high among those adolescents who are more open to smoking⁹², it is important that initiation of nicotine use should not be facilitated but discouraged amongst young people. 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.

Conclusion

- E-cigarettes are primarily used by smokers and smokers considering to stop smoking, as well as by former smokers. Adolescent users of e-cigarettes usually smoke, too.
- Above all, e-cigarettes are used as an alternative to conventional cigarettes and to stop smoking due to its' attributed less harmful health hazard.
- Although e-cigarettes are used by very few non-smokers, they probably could tempt to smoke conventional cigarettes.

6 Efficacy as cessation device

6.1 User opinions

Many consumers believe that electronic cigarettes are helpful in an attempt to quit smoking: More than two thirds of users are using the products to cut down or quit smoking or to mitigate withdrawal symptoms^{26,41,42,51,63}.

In an Internet survey involving 3,587 participants from more than five countries (U.S.A., France, United Kingdom, Switzerland, Canada and others), which used a questionnaire published on the Swiss smoking cessation website Stop-Tabak.ch, 77 percent of participants said they were using the e-cigarette to quit smoking or avoid relapsing; 79 percent want to reduce craving in a cessation attempt and 67 percent are using it to reduce withdrawal symptoms⁴². There are also many young people who believe that e-cigarettes could be helpful to quit smoking²¹.

A survey with eleven respondents recruited in an e-cigarette internet forum revealed the following five main reasons that electronic cigarette users consider, why these products are helpful in smoking cessation: The feeling is similar to that of smoking (imitating smoking) (1), you can maintain the habit and it turns into a sort of hobby (2) where you can share experiences with like-minded people (3), you can identify yourself as a "vaper" (4), and the switch to electronic cigarettes makes you feel like having quit smoking (5). Compared to nicotine replacement products, respondents think electronic cigarettes have the additional advantage of not having any side effects and that they are more likely to prevent relapse. Survey participants hence consider electronic cigarettes capable of facilitating smoking cessation by switching to a less harmful product without having to forego nicotine and the habit⁵.

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

Electronic cigarettes can reduce craving and withdrawal symptoms. According to two Internet surveys, 70 to 90 percent of electronic cigarette consumers have less desire to smoke when using electronic cigarettes^{26,42}. About 70 to 80 percent of respondents also report that using electronic cigarettes reduces mood swings such as irritability, nervousness, restlessness or depressed mood as well as difficulty concentrating.

Electronic cigarettes are more effective in reducing withdrawal symptoms in former smokers than in current smokers. It is remarkable that electronic cigarettes without nicotine also reduce craving and withdrawal symptoms, albeit to a slightly lesser extent than do nicotine-containing devices⁴² (Fig. 6.1).

The finding that not only electronic cigarettes with nicotine-containing liquids are capable of alleviating withdrawal symptoms^{39,121-123} but that nicotine-free products can do so, too^{10,25,42}, suggests that the way in which electronic cigarettes are used, which strongly resembles that of conventional smoking, plays an important role for this effect. Apparently, the mere holding of the product, sucking at it and inhaling the aerosol already mitigate withdrawal symptoms.

Although electronic cigarettes are substantially less effective in suppressing the desire to smoke than conventional cigarette smoking^{10,39,121}, they perform comparably to nicotine inhalers. However, the test persons perceived using e-cigarettes as more satisfying than using an inhaler¹⁰ (Fig. 6.2).

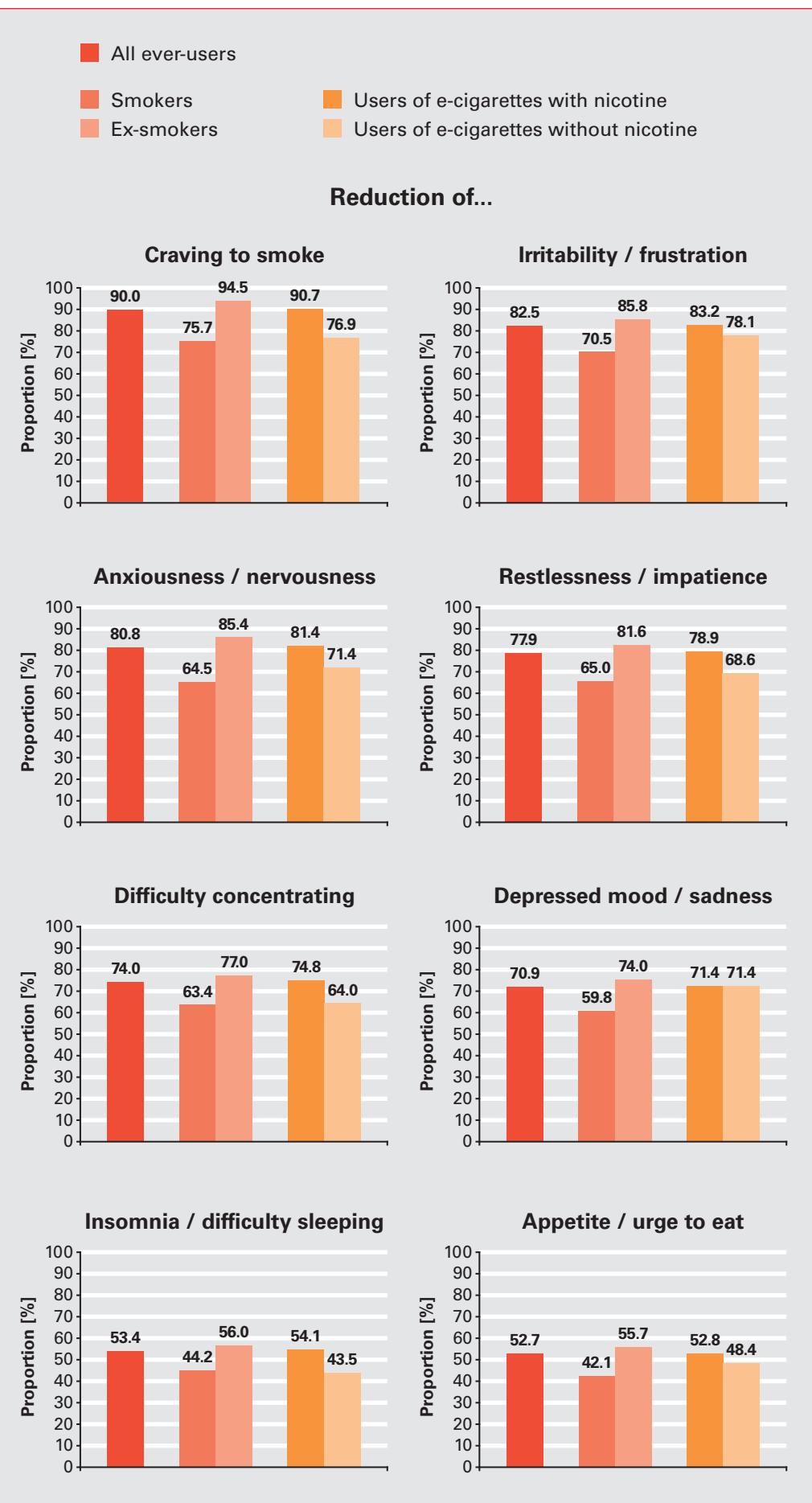


Figure 6.1
Reduction of craving and withdrawal symptoms due to use of electronic cigarettes.
Source: Etter & Bullen 2011⁴²
Illustration: German Cancer Research Center 2013

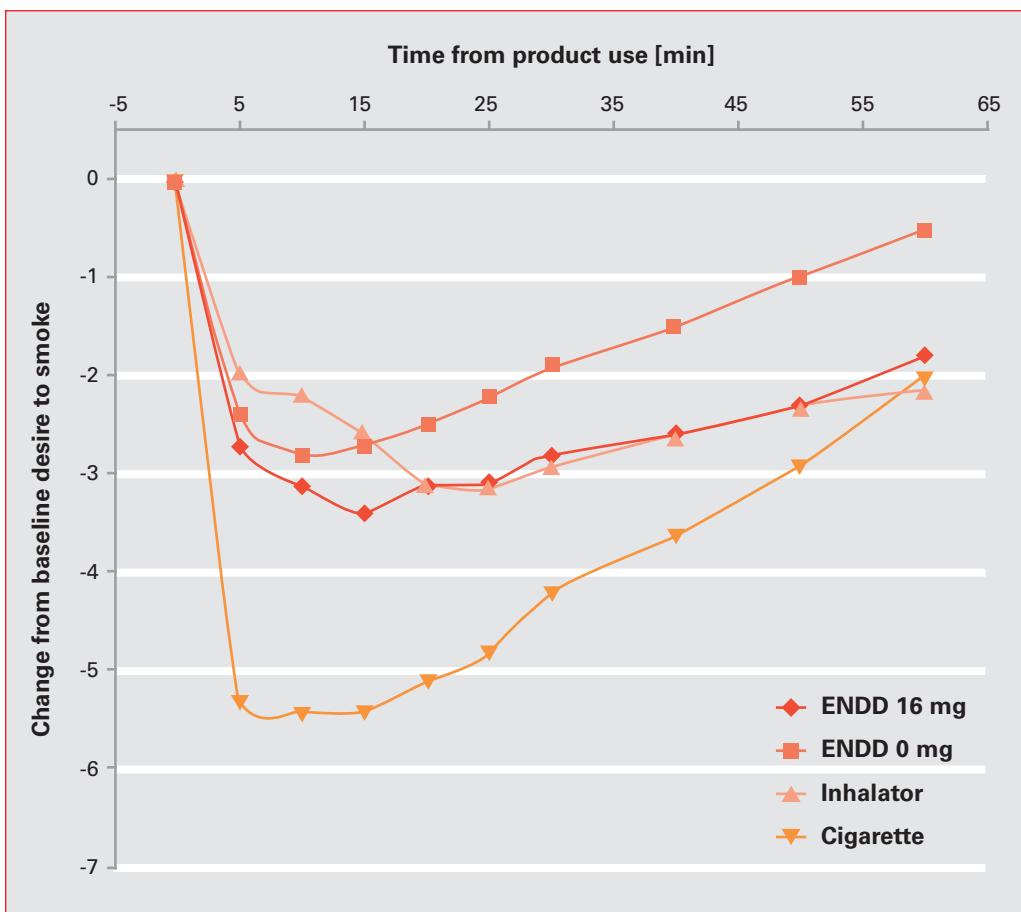


Figure 6.2
Suppression of desire to smoke resulting from electronic cigarettes with and without nicotine, nicotine inhaler and conventional cigarettes.
Participants rated their desire to smoke on a scale from zero to ten.
Source: Bullen 2010¹⁰
Illustration: German Cancer Research Center 2013

6.3 Efficacy of electronic cigarettes for sustained tobacco cessation

Even though electronic cigarettes can suppress withdrawal symptoms, evidence is still lacking whether they also achieve sustained smoking cessation effectively. To date, the following studies have been conducted on the efficacy of electronic cigarettes as a long-term smoking cessation aid: one prospective cohort study⁹³, several surveys on consumption behaviour and smoking cessation, mostly conducted online^{26,41,42,51,63,104,113}, as well as one case report¹⁷. The design of these studies does not qualify them to provide evidence of the efficacy of electronic cigarettes in tobacco cessation. They are not representative and partly not independent. The results of several studies cannot be generalized because the number of participants is too small¹⁷ or participants are selective^{26,41,42,51,63,104,113} and the author of one study works as a consultant for a company which markets electronic cigarettes⁹³. To date, there is not a single study available based on reliable methods (randomized controlled study)

with a large number of participants and sufficiently long observation period to provide evidence of the efficacy of the electronic cigarette as cessation device. According to the surveys, over two thirds of respondents are using electronic cigarettes to reduce or quit smoking or to prevent relapse. More than 90 percent of consumers perceive the devices as helpful in smoking cessation^{42,51}; only in the smallest of the surveys, no more than 20 out of 81 participants said this was so⁴¹. Due to the way in which participants were recruited in the above three of the studies, such as in user forums, on websites where electronic cigarettes are sold, or at a user meeting, it cannot be excluded that disproportionately more enthusiastic users participated and hence that the overall satisfaction with the product may be overestimated. In an online survey with 1,347 participants from 33 countries (mostly European) recruited through the websites of two popular e-cigarette vendors, 74 percent of participants reported not having smoked any conventional cigarettes for several weeks or months since they started using e-cigarettes, and 14 percent said they had substantially reduced smoking²⁶.

According to a survey with responses of 216 first-time buyers of e-cigarettes, about two thirds of participants (66.8 percent) reduced cigarette consumption, almost half of them (48.8 percent) were temporarily smoke-free and 31 percent of users reported being completely smoke-free within six months after starting to use e-cigarettes. Most of these former smokers (56.7 percent) continue using electronic cigarettes; only about one third of them have stopped using nicotine-containing products¹⁰⁴. However, it cannot be excluded that considerably more successful ex-smokers have completed the questionnaire than have e-cigarette consumers who continue smoking. The real success rate may therefore be significantly lower.

The case study reports about three heavy smokers, who had already tried to quit several times and failed. They were smoke-free for at least six months after starting to use e-cigarettes. However, only one of them also quit using the e-cigarette after some time¹⁷.

In a small prospective cohort study, smokers with no intention to quit were supplied with electronic cigarettes for 24 weeks. At the end of the study, 13 out of originally 40 participants had cut down smoking by 50 percent; nine percent had stopped smoking, with six of them continuing to be regular e-cigarette users⁹³. However, as one third of participants dropped out in the course of the study, the final evaluation included only the data of 27 individuals. It cannot be excluded that the participants who dropped out were mainly those who were dissatisfied with the devices and continued smoking. In this case, smoking cessation success rate would be lower than assumed in the study. According to a survey commissioned by the European Commission, at present the devices neither seem to be popular for smoking cessation nor do they show much efficacy. In Germany, only seven percent of smokers intending to quit say they are using electronic cigarettes as a smoking cessation aid. By contrast, 17 percent of smokers trying to quit are using pharmaceutical nicotine replacement products and a majority of them (66 percent) try to quit smoking without any aids and succeed in doing so. 75 percent of successful ex-smokers report having quit without any aids; six percent managed to quit with the aid of nicotine replacement products and none of the ex-smokers report having become smoke-free with the aid of electronic cigarettes¹¹³. Since the survey was based on

a random sample, it does not necessarily reflect the ratio of smokers, former smokers and non-smokers in the population. In addition, the sample may have been too small to adequately capture the small proportion of e-cigarette consumers in the population. Both factors may distort the results obtained.

To sum up, although available studies suggest that electronic cigarettes can reduce the urge to smoke and withdrawal symptoms, and even though some smokers switch – at least temporarily – from conventional cigarettes to the electronic devices, only a very small proportion of smokers seems to achieve sustained cessation of nicotine consumption in this way. Based on current data, the long-term duration of a switch or cessation is not clear, because currently available studies cover only a maximum time period of six months. However, relapse after smoking cessation is not uncommon after much longer time periods. Although the desire to smoke does subside over time after smoking cessation, one third of ex-smokers still feels a certain need to smoke even after one year¹²⁰.

Generally, it is a matter of concern that most smokers trying to quit with the aid of electronic cigarettes may quit smoking but will still continue consuming nicotine. This is a big problem not only because of the technical product flaws described in Chapter 2, but also because the long-term health risks involved are unclear. Moreover, the goal of tobacco cessation, from an addiction therapy perspective, is to withdraw completely from the addiction. This is not achieved when smokers switch to or continue smoking electronic cigarettes with nicotine. Instead, nicotine dependence and addictive behaviour are maintained.

Conclusion

- Electronic cigarettes can reduce craving and withdrawal symptoms.
- Even e-cigarettes containing no nicotine reduce the desire to smoke and withdrawal symptoms.
- Some smokers cut down smoking or quit smoking as a result of using e-cigarettes.
- The efficacy of e-cigarettes as an aid for sustained smoking cessation has not yet been proven.
- We urgently need to know more on the efficacy of electronic cigarettes as a cessation device. Carefully planned studies by qualified and objective scientists are necessary.

7 Product Regulation

At the present time, electronic cigarettes are marketed in Germany in a legal limbo without any proof of product safety or functionality, because the question of which legal regulations should apply to these products is controversial. Many questions regarding product safety and function of electronic cigarettes are still open. Therefore, based on current knowledge, the electronic cigarette cannot be rated as a harmless product, even though it may contain fewer harmful substances than conventional cigarettes, which are very harmful. Until proof is provided that the products do not involve any health risks, their sale is an uncontrolled experiment, possibly at the cost of consumers' health. To ensure consumer protection, we therefore need clarity in Germany as to the application of regulations for electronic cigarettes. The following regulatory areas need to be discussed:

1. Product classification
2. Product safety
3. Use in public places
4. Youth protection
5. Advertising

7.1 Product classification

7.1.1 Possible classifications

It is currently a legal dispute which product category e-cigarettes should be placed into. Possible categories under discussion include medicinal products, medical devices, consumer products, tobacco products or food.

■ Medicinal product

The most convincing proposed classification is the one placing e-cigarettes into the category of medicinal products by presentation and/or function.

E-cigarettes can be regarded as medicinal products by presentation, because the way they are presented often gives consumers with average background knowledge the impression that the e-cigarette, regardless of nicotine content, is as a medicinal product for tobacco cessation. This impression results, for example, from the advertising of qualities normally associated with a medicinal product ("German pharmaceutical laboratory"¹⁰⁸, "German pharmacy"¹⁰⁸, "harm reduction"¹⁰⁹, "facilitation of cessation"²⁸, advertising by specialist associations³³). The regulation for medicinal products by presentation is also intended to protect consumers from products that are used instead of appropriate remedies or effective (including non-medicinal) medical treatment options⁴⁶. Moreover, one approach in tobacco cessation is stepwise reduction of nicotine intake. For this purpose, conventional nicotine replacement therapy uses products with varying nicotine levels. Electronic cigarettes are also available with different nicotine levels and also include products with very low nicotine levels and those containing no nicotine at all. Electronic cigarettes differ from already authorised nicotine replacement products in an important aspect: the way in which nicotine is delivered. Electronic cigarettes are consumed like smoking tobacco so that the smoking habit and the characteristic smoking process are initially maintained. Thus, even products containing no nicotine are capable of suppressing withdrawal symptoms^{10,25,42}. Consequently, such low-nicotine and nicotine-free products are part of the therapy process and hence need to be regulated in the same way as products with higher nicotine levels. Hence, classification of electronic cigarettes as medicinal products by presentation is appropriate, particularly considering

that it is sufficient for a medicinal product to give the impression of also helping to relieve symptoms.

In addition, e-cigarettes containing nicotine should be regulated as medicinal products by function, because nicotine has a pharmacological effect exceeding the relevance threshold required for classification. Moreover, the whole range of product characteristics needs to be considered for classification as a medicinal product. In particular, it needs to be taken into account that consumers use e-cigarettes like nicotine replacement products because both partly have similar functions. Furthermore, there is substantial danger for consumers because of the potentially toxic/fatal effect of ingested high concentration nicotine liquid. Considering all this, it is appropriate to classify (nicotine-containing) electronic cigarettes as medicinal products by function.

■ Medical device

While medicinal products act mainly by pharmacological, metabolic or immunological means, medical devices exert their effect by mechanical and/or physical means. The e-cigarette bodies (atomizer etc.) are marketed together with the liquids, but as a loose unity. The technical components of e-cigarettes (delivery system) are subject to the regulations pertaining to medical devices, because they are used for administering a medicinal product.

■ Consumer product

There are plans to classify some e-cigarettes – at least those below a certain nicotine threshold value – as normal consumer products (cf. European Commission 2012⁴⁵). However, since nicotine always exerts a pharmacological effect on the body and e-cigarettes (independent of nicotine content) are presented as (seeming) medicinal products, the German Cancer Research Center advocates their classification as medicinal products.

■ Tobacco product

Electronic cigarettes usually do not contain any tobacco. Therefore, they do not fulfil requirements to be classified as tobacco products.

■ Food

Classification of e-liquids as food is out of the question. Food is any substance or product that is to be processed, partially processed, or unprocessed for

consumption and is intended to be, or reasonably expected to be, ingested by humans. This refers to intake via the gastrointestinal tract⁸⁷. However, this is not the case with e-cigarettes. Moreover, nicotine is not approved as food under food law regulations.

E-cigarettes, regardless of their nicotine content, should be classified as medicinal products. Hence, e-cigarettes, regardless of their nicotine content, may only be marketed if they have been approved according to Directive 2001/83/EC, i.e. according to drug approval regulations.

7.1.2 Regulation of e-cigarettes at international level

Regulation of e-cigarettes varies strongly at international level:

Manufacture, import and sale of electronic cigarettes have been prohibited in Brazil, the Seychelles, Singapore and Uruguay. The Seychelles and Singapore have classified e-cigarettes as imitation products. Other countries only regulate individual areas: production or sale or advertising²³.

In the U.S.A., tobacco products are regulated under the Family Smoking Prevention and Tobacco Control Act of 2009. It defines the term "tobacco product" as any product which is made or derived from tobacco and which is not a drug, medical device or combination product. Between 2008 and 2010, the U.S. Food and Drug Administration as the responsible authority determined that certain e-cigarettes were unapproved combination products (drug/medical device) and refused admission to those offered for import by a number of manufacturers. A court decided that e-cigarettes and other products made or derived from tobacco can be regulated as "tobacco products" under the Act and are not drugs/devices unless they are marketed for therapeutic purposes. FDA plans to take measures to ensure that all tobacco products and all other products made or derived from tobacco are made subject to appropriate regulatory mechanisms¹¹⁸.

In Canada, e-cigarettes are subject to the Food and Drugs Act. Products regulated under this Act require market admission to be imported to Canada or to be advertised or sold in Canada. To date, no e-cigarettes have been admitted for sale in Canada⁶².

In European countries, e-cigarettes have either not yet been regulated (e.g. Ireland, Lithuania, Spain, United Kingdom) or are often classified as medicinal products depending on their marketing as tobacco cessation aids (e.g. Belgium, France, Luxemburg, Austria, Slovenia, Czech Republic, Cyprus) and/or depending on their nicotine content. In Belgium and Luxemburg, for example, e-cigarettes are classified as medicinal products if they contain nicotine without tobacco extract. In Denmark, Estonia, the Netherlands and Austria, they are regarded as medicinal products if they contain any nicotine and in France, classification depends on the amount of nicotine contained. In some countries such as Greece, e-cigarettes are prohibited unless explicitly approved. In Norway, all new products containing tobacco or nicotine are prohibited and in Lithuania, all imitation products are prohibited⁴⁴ (see Table. 7.1).

7.2 Product safety

To protect consumers, various measures need to be taken to establish product safety, including for long-term use of the product. The World Health Organization demands that manufacturers provide evidence of product safety and regulatory authorities should verify this evidence¹³⁰. Evidence of product safety requires the following measures, in particular:

- Exact disclosure of ingredients of liquids on the packaging (purity, stability)
- Assessment of exposure to ingredients for short-term and long-term use of electronic cigarettes
- Toxicological evaluation of inhaled intake of all ingredients for short-term and long-term use
- Assessment of health risks associated with short-term and long-term use of electronic cigarettes
- Assessment of addictive potential of nicotine-containing products
- Assessment of exposure of third parties (second-hand exposure, passive vaping)

If electronic cigarettes were classified as medicinal products, the strict approval procedure in place for this type of product would ensure high safety standards of the products for consumers. Insofar as product safety standards demanded by the WHO are not covered by the approval procedure for medicinal products, such as assessment of second-hand exposure,

these investigations must additionally be conducted by an appropriate scientific institute (e.g. by the German Federal Institute for Risk Assessment, Bundesinstitut für Risikobewertung, BfR).

7.3 Use in public places

Germany does not yet have a uniform regulation of e-cigarette use in public places. The Federal Government holds that e-cigarettes are generally subject to the Federal Non-Smoker Protection Act (Bundesnichtraucherschutzgesetz)¹⁴. In the Federal States of Baden-Württemberg⁷⁴, Hessen⁶⁵ and Rhineland-Palatinate¹¹¹ as well as in the draft law of 26 June 2012 for North Rhine-Westphalia amending the existing non-smoker protection law⁷⁵, electronic cigarettes are considered equal to conventional cigarettes as far as non-smoker protection is concerned. The German national railway company, Deutsche Bahn, also considers e-cigarettes subject to non-smoker protection regulations and prohibits use of e-cigarettes on their trains²⁹.

The German Cancer Research Center supports equal treatment of e-cigarettes in non-smoker protection legislation. Article 8 of the WHO Framework Convention on Tobacco Control (FCTC), ratified by Germany, regulates protection from exposure to tobacco smoke. This provision should be made applicable to e-cigarettes as well. Since health risks for third parties due to exposure to emissions from e-cigarettes cannot be excluded at the present time and health protection and addiction policies should make smoking in public less normal, e-cigarettes should be treated the same as conventional cigarettes in matters of non-smoker protection. Moreover, it is only by treating them the same that we can ensure for existing non-smoker protection laws to be executed, because e-cigarettes imitate normal cigarettes in their appearance and handling, which would make effective control difficult due to their outward resemblance.

The Federal German Institute for Risk Assessment has assessed a number of typical ingredients of e-cigarette liquids such as nicotine, vaporizing agents, additives and flavours. It has reached the conclusion that, based on current knowledge, health risk from second-hand exposure cannot be excluded (cf. BfR press release 17/2012 of 7 May 2012¹¹). The BfR therefore also

Country	Regulation of nicotine containing products (electronic cigarettes and possible other products)
Austria	Regarded as medicinal products by function if the product contains nicotine or other pharmacologically active substances; if the product is promoted for smoking cessation or treatment of nicotine addiction, the product is regarded as medicinal products by presentation; in this case the apparatus is also regulated as a medical device.
Belgium	Considered as tobacco products if it contains tobacco extract; considered as pharmaceuticals by function if it contains nicotine without containing tobacco extract; considered to be pharmaceutical by presentation if, even without nicotine, there are claims that it helps to quit smoking.
Bulgaria	Not regulated as a pharmaceutical or medicine device by legislation. The scope of the TPD has to be widened. The future Directive have to forbid each novel tobacco or tobacco imitative product and should list the old and already approved tobacco products.
Cyprus	Regarded as medicinal products by presentation provided they are sold as a product to quit smoking. In the market there are also nicotine containing products which are not regarded as medicinal products but rather nicotine consumer or leisure products. Such products are not regulated.
Czech Republic	Electronic cigarettes are not regulated explicitly as regards status of product: If presented as a product for tobacco cessation treatment - considered as pharmaceuticals in combination with medical device (however, no registered electronic cigarette in this regard so far). If this function not presented - general product safety law applies. Sale of electronic cigarettes to minors (less than 18 years old) is prohibited.
Denmark	With nicotine regulated as pharmaceuticals due to the pharmacological function of the nicotine.
Estonia	Electronic cigarettes are regarded as pharmaceuticals if with nicotine.
Finland	Nicotine cartridges are classified as medicinal products by function; possible ban coming on all nicotine products other than medicine and pesticides.
France	If presented as cessation treatment, whatever the nicotine dosage, the product is regarded as a medicinal product. If not presented as cessation treatment, regarded as a medicinal product by function if the quantity of nicotine within the vial is equal or above 10 mg nicotine or if the refill solution has a nicotine concentration equal or above 20 mg/ml. If not medicinal products according to the description above, the General Product Safety Directive applies.
Germany	Nicotine containing liquids in electronic cigarettes have been qualified as medicinal products (a few special products). Therefore, a marketing authorization according to the German Medicinal Products Act is required prior to any marketing of these products. No marketing authorizations for electronic cigarettes have been granted yet. Without this authorization a marketing would be unlawful. The execution of the German Medicinal Products Act falls within the competencies of the German Federal States. Accordingly, if the Federal States authorities notice an unlawful sale or offering of electronic cigarettes (containing nicotine) they ought to prohibit it. There are currently court proceedings pending regarding the classification of electronic cigarettes as medicinal products.

Table 7.1
**Regulation of E-cigarettes
in European countries.**

Source: European
Commission 2012⁴⁴

Country	Regulation of nicotine containing products (electronic cigarettes and possible other products)
Greece	Prohibited under the new tobacco legislation unless approval by the Ministry of Health.
Hungary	Not regulated explicitly, but regarded as medicinal products by function.
Iceland	Regarded as medicinal products both by presentation and function.
Ireland	Not regulated.
Italy	Electronic cigarettes are not regarded as medicinal products in Italy.
Latvia	Electronic cigarettes are not specially regulated. They follow the rules as for all consumers' products.
Lithuania	No specific legislation, but all imitation products are banned by the Law on Tobacco Control. The ban also covers non-nicotine products.
Luxembourg	Considered as tobacco products, if they contain tobacco extracts; considered as pharmaceuticals by function and/or presentation, if they contain nicotine without containing tobacco extract, and/or if presented as cessation treatment; electronic cigarettes not yet regulated specifically (probably they will be considered as pharmaceutical).
Malta	With nicotine, regulated under tobacco act – requirements for labelling, no advertising, no cessation claims and smoke-free environments requirements apply.
Netherlands	Considered pharmaceutical by function or presentation if it contains nicotine.
Norway	New products with tobacco or nicotine are prohibited.
Poland	Electronic cigarettes are not regarded as medicinal products. Advertising of these products is banned.
Portugal	Electronic cigarettes containing nicotine should be regarded as medicinal products by presentation and/or function.
Romania	Regarded as medicinal products by function.
Slovakia	Regarded as medicinal products by function. Total ban on selling and smoking electronic cigarettes in public places such as schools, bus stations, hospitals and cinemas. Smoke-free environments.
Slovenia	If presented as cessation treatment, regulated as pharmaceuticals; if not, covered by the General Product Safety Directive.
Spain	No specific regulation. Electronic cigarettes have been considered recreational consumer products without therapeutic indications.
Sweden	Products containing purely nicotine are generally classified as medical products. The Medical Products Agency classifies the ampoules/filters of "electronic cigarettes", but not the "cigarette" itself. The classification applies irrespective of the intended use, as stated by the seller. The products need approval as medicinal products and can only be sold at certain premises.
United Kingdom	Not regulated at present (other than by General Product Safety Directive). Consideration is being given to regulation of all nicotine containing products as medicinal products by function.

recommends that the use of all e-cigarettes in smoke-free areas should be banned and that these products should be treated like conventional cigarettes to ensure adequate protection of non-smokers (cf. BfR press release 17/2012 of 7 May 2012¹¹).

7.4 Youth protection

The German Cancer Research Center demands that e-cigarettes should be classified as medicinal products. The law does not generally prohibit that pharmacies dispense medicinal products to children and youth. However, according to § 13, 2 of the pharmacists' professional code of conduct of the Pharmacists' Association of the State of Baden-Württemberg (Landesapothekerkammer Baden-Württemberg), pharmacists have a special responsibility when dispensing medicinal products and medical devices to children, youth and individuals with restricted capacity of discernment. For quality assurance, the Federal Union of German Associations of Pharmacists (Bundesapothekerkammer, ABDA) has issued an information sheet on the dispensing of medicinal products to children (last revised 2 March 2011). Hence, pharmacies are obliged to act with particular care when dispensing medicinal products to children and youth.

In view of the fact that § 10 of the German Youth Protection Act (Jugendschutzgesetz) prohibits the dispensing of tobacco products to children and youth, the same should apply to the dispensing of medicinal products to children and youth. If an adult sends a child or an adolescent to collect drugs, for example because of being bed-ridden, pharmacies should at least advise the adult of the availability of the pharmacy's delivery service by calling or sending a written note.

7.5 Advertising

Since e-cigarettes, regardless of their nicotine content, should be classified as

medicinal products, the German Law on Advertising in the Healthcare Sector (Heilmittelwerbegesetz – HWG)³¹ should apply for their advertising. The HWG differentiates between trade advertising (targeting professional circles such as physicians and pharmacists) and consumer advertising (targeting the public). Advertising of medicinal products is subject to specific provisions. Among other things, advertising of medicinal products must generally not be misleading (§ 3 HWG) and must contain certain information (cf. § 4 HWG). For medicinal products for treating nicotine addiction, advertising may refer, even outside professional circles, to the detection, prevention, cure or mitigation of the diseases or conditions in humans listed in the Annex (cf. § 12 HWG in conjunction with A No. 3 of Annex for § 12 A).

E-cigarettes should therefore be treated equal to nicotine replacement products available on the market concerning the regulation of advertising. Hence, the German Law on Advertising in the Healthcare Sector (Heilmittelwerbegesetz – HWG)³¹ should be applied.

Conclusion

- Electronic cigarettes, regardless of their nicotine content (including nicotine-free products), may only be marketed if they have been approved according to Directive 2001/83/EC or the German Medicinal Products Act (Arzneimittelgesetz, AMG), respectively, i.e. as medicinal products. This makes them subject to the necessary high safety standards.
- The e-cigarette body (atomizer etc.) should be classified as a medical device.
- Classification of e-cigarettes as medicinal products makes them subject to the German Law on Advertising in the Healthcare Sector (Heilmittelwerbegesetz, HWG).
- E-cigarettes should not be dispensed to children and youth, not even if classified as medicinal products.
- Non-smoker protection legislation should generally treat e-cigarettes equal to conventional cigarettes.

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