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on Tobacco Control**

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**Electronic Nicotine Delivery Systems and Electronic
Non-Nicotine Delivery Systems (ENDS/ENNDS)**

Report by WHO

INTRODUCTION

1. This document was prepared in response to the request¹ made by the Conference of the Parties (COP) at its sixth session (Moscow, Russian Federation, 13–18 October 2014) to the Convention Secretariat to invite WHO to: (a) prepare a report on Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS) for the seventh session of the COP (COP7), covering updates on the evidence of the health impact of ENDS/ENNDS, their potential role in tobacco cessation and impact on tobacco control efforts; (b) subsequently assess policy options to achieve the objectives outlined in paragraph 2 of decision FCTC/COP6(9); and (c) consider the methods to measure the contents and emissions of these products. Following the terminology approved by COP, this report differentiates between ENDS and ENNDS depending on whether or not the heated solution delivered as an aerosol by the device contains nicotine.

2. This report incorporates the December 2015 deliberations and scientific recommendations on ENDS/ENNDS by the WHO Study Group on Tobacco Product Regulation (TobReg) at its eighth meeting (Rio de Janeiro, Brazil, 9–11 December 2015)², the May 2016 informal consultation on policy options held in Panama (4–5 May 2016, Panama City, Panama) and four background papers commissioned by WHO^{3,4,5,6}. This report does not consider methods to measure the contents and emissions of ENDS/ENNDS. All appendices to this report can be found on the WHO websiteⁱ.

ENDS/ENNDS PRODUCTS

3. All ENDS/ENNDS heat a solution (e-liquid) to create an aerosol which frequently contains flavourants, usually dissolved into Propylene Glycol or/and Glycerin. All ENDS (but not ENNDS) contain nicotine. Although generally considered a single product class, these products constitute a diverse group with potentially significant differences in the production of toxicants and delivery of nicotine. There are several coexisting types of devices on the market: first-generation or so-called cigalikes, second-generation tank systems and even larger third-generation or personal vaporizers. Others classify these devices into closed and open systems depending mainly on the degree of control that users have over the e-liquid used and the voltage and resistance applied to heating the e-liquid and ventilation features.

4. The choice of e-liquid, the user's puffing style and the device's capacity to aerosolize the e-liquid at increasing temperatures by modulating its wattage and resistance will all determine whether the use of ENDS/ENNDS produces a satisfactory experience to the user in terms of the speedy delivery of sufficient nicotine to mimic the sensory feel of smoking.

ⁱ http://who.int/tobacco/industry/product_regulation/electronic-cigarettes-report-cop7/en/index.html

POTENTIAL ROLE OF ENDS/ENNDS IN TOBACCO CONTROL

5. If the great majority of tobacco smokers who are unable or unwilling to quit would switch without delay to using an alternative source of nicotine with lower health risks, and eventually stop using it, this would represent a significant contemporary public health achievement. This would only be the case if the recruitment of minors and non-smokers into the nicotine-dependent population is no higher than it is for smoking, and eventually decreases to zero. Whether ENDS/ENNDS can do this job is still a subject of debate between those who want their use to be swiftly encouraged and endorsed on the basis of available evidence, and others who urge caution given the existing scientific uncertainties as well as the performance variability of products and the diversity of user behaviour.

ENDS/ENNDS MARKET SIZE

6. The global market for ENDS/ENNDS in 2015 was estimated at almost US\$ 10 billion. About 56% was accounted for by the United States of America and 12% by the United Kingdom. Another 21% of the market was divided between China, France, Germany, Italy and Poland (3–5% each)⁷. It is unclear whether the sales of ENDS/ENNDS will continue to increase⁸. In addition, the market may change since the tobacco industry has launched alternative nicotine delivery systems that heat but do not burn tobacco^{9,10,11}, and is developing or has bought nicotine inhaler technology that does not require a heating mechanism^{12, 13,14}.

HEALTH RISKS OF EXCLUSIVE ENDS/ENNDS USEⁱⁱ

7. The typical use of unadulterated ENDS/ENNDS produces aerosol that ordinarily includes glycols, aldehydes, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbon (PAHs), tobacco-specific nitrosamines (TSNAs), metals, silicate particles and other elements. Dicarboxyls (glyoxal, methylglyoxal, diacetyl) and hydroxycarbonyls (acetol) also are thought to be important compounds in the aerosol. Many of these substances are toxicants that have known health effects resulting in a range of significant pathological changes.

8. The number and level of known toxicants generated by the typical use of unadulterated ENDS/ENNDS is on average lower or much lower than in cigarette smoke, with a few new toxicants specific to ENDS such as glyoxal. However, the levels of toxicants can vary enormously across and within brands and sometimes reach higher levels than in tobacco smoke¹⁵. This is probably due, among other things, to the increased thermal decomposition of e-liquid ingredients with rising applied temperatures in open system devices.ⁱⁱⁱ A number of metals - including lead, chromium, and nickel and formaldehyde^{15,16} - have been found in the aerosol of some ENDS/ENNDS at concentrations equal to or greater than traditional cigarettes under normal experimental conditions of use.

9. ENDS aerosol contains nicotine, the addictive component of tobacco products. In addition to dependence, nicotine can have adverse effects on the development of the foetus during pregnancy and may contribute to cardiovascular disease. Although nicotine itself is not a carcinogen, it may function as a “tumour promoter” and seems to be involved in the biology of malignant diseases, as well as of neurodegeneration¹⁷. Foetal and adolescent nicotine exposure may have long-term consequences for brain development, potentially leading to learning and anxiety disorders^{18,19,20}. The evidence is sufficient to warn children and adolescents, pregnant women, and women of reproductive age against ENDS use and nicotine.

10. Close to 8,000 e-liquid unique flavours²¹ have been reported. The health effects of heated and inhaled flavourants used in the e-liquids have not been well studied.²² Heated and inhaled popcorn^{23,24},

ⁱⁱ See also Appendix 1 on other health risks to be considered.

ⁱⁱⁱ Other possible explanations for this variance are the potential for the heating element and associated components to shed metallic and other particles on heating and the unpredictability of some of the analytical methods used, since very few have been standardized and validated for analysing ENDS/ENNDS.

cinnamon²⁵ and cherry flavourants are potentially hazardous, with the limited literature on the topic indicating that most flavourants may pose appreciable health risks from long-term use, especially those that are sweet. Many are irritants^{26,27,28} which may increase airway inflammation²⁹; some are more cytotoxic than unflavoured aerosol although less so than tobacco smoke³⁰, or increase the susceptibility of airway cells to viral infection after direct contact with e-liquid³¹, although the relevance of direct effects of contact with e-liquid, as opposed to aerosol, is unclear³².

11. Based mostly on the levels and number of toxicants produced during the typical use of unadulterated ENDS/ENNDS made with pharmaceutical-grade ingredients, it is very likely that ENDS/ENNDS are less toxic than cigarette smoke. However, ENDS/ENNDS are unlikely to be harmless, and long-term use is expected to increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking³³. The magnitude of these risks is likely to be smaller than from tobacco smoke^{34,35,36}, although there is not enough research to quantify the relative risk of ENDS/ENNDS over combustible products. Therefore, no specific figure about how much “safer” the use of these products is compared to smoking can be given any scientific credibility at this time. Existing modelling studies indicate, however, that in order for there to be a potential population-wide net health benefit from ENDS/ENNDS at present usage rates, these products would need to be at least three times “safer” than cigarettes^{37,38}.

12. There is an urgent need to elucidate the range of relative risks when using the diverse ENDS/ENNDS devices and e-liquids, and about user behaviour compared to smoking and use of other nicotine products, recognizing that:

- a. complex mixtures, such as in ENDS liquids and aerosol, have the potential for toxicological effects even if toxicants are at low or very low concentrations³⁹;
- b. predicting adverse health effects of these complex mixtures solely on the basis of aerosol composition might prove futile without solid evidence from the coordinated use of chemical, *in vitro*, clinical³⁹ and epidemiological methods; and that
- c. simple comparisons of toxicant levels in ENDS/ENNDS aerosol to the high levels in tobacco smoke, as advocated by the tobacco industry^{40,41}, may be of little value given the absence of science on safe tolerance limits for smoke constituents or their specific effects on the multiple diseases caused by smoking.

HEALTH RISKS TO BYSTANDERS FROM EXPOSURE TO EXHALED AEROSOL FROM ENDS/ENNDS USERS

13. A recent systematic review of the health risks from passive exposure to exhaled aerosol from ENDS/ENNDS users - or second-hand aerosol (SHA) - concluded that “the absolute impact from passive exposure to electronic cigarette vapour has the potential to lead to adverse health effects⁴².” A WHO-commissioned review³ found that while there are a limited number of studies in this area^{43,44,45,46,47,48,49,50,51,52,53,54,55}, it can be concluded that SHA is a new air contamination source for particulate matter, which includes fine and ultrafine particles, as well as 1,2-propanediol, some VOCs, some heavy metals, and nicotine.

14. The levels of some metals such as nickel and chromium are higher in SHA from ENDS than in second-hand smoke (SHS) and certainly background air. Compared to air background levels, PM 1.0 and PM 2.5 in SHA are between 14 and 40 times, and between 6 and 86 times higher respectively^{iv}. In addition, nicotine in SHA has been found between 10 and 115 times higher than in background air levels, acetaldehyde between two and eight times higher, and formaldehyde about 20% higher. Except for heavy metals, these compounds are generally found at lower concentrations than those found in SHS. At present, the magnitude of health risks from higher than background levels of these compounds and elements are empirically unknown.

^{iv} Particle matter from SHA, however, tend to be in the air a shorter time than from SHS and it is not clear what could have a health effect, whether it is its concentration or its composition (which is different from PM in SHS).

15. While some argue that exposure to SHA is unlikely to cause significant health risks⁵⁶, they concede that SHA can be deleterious to bystanders with some respiratory pre-conditions⁵⁷. It is nevertheless reasonable to assume that the increased concentration of toxicants from SHA over background levels poses an increased risk for the health of all bystanders⁵⁸.

ABILITY OF ENDS/ENNDS TO AID SMOKERS TO QUIT SMOKING

16. The scientific evidence regarding the effectiveness of ENDS/ENNDS as a smoking cessation aid is scant and of low certainty, making it difficult to draw credible inferences. A 2014 review⁵⁹ based on two randomized clinical trials (RCTs) concluded that although the analyzed ENDS had a similar, although low, efficacy for quitting smoking, the overall quality of the evidence was low⁶⁰. The WHO-commissioned review reached similar conclusions about the RCTs' quality of evidence and efficacy.

17. Longitudinal studies are more abundant and better reflect "real world" conditions of use than RCTs, but present more methodological concerns. Two reviews of these studies suggest that the use of ENDS may reduce the chances of quitting smoking^{61,4}. However, the evidence is of very low certainty. Although most longitudinal studies found no cessation benefit or a diminished cessation benefit associated with use of ENDS, a few studies^{62,63} found that the use of third generation ENDS under specific conditions of frequency of use may have cessation benefits. This needs to be further explored before reaching any final conclusions. In summary, given the scarcity and low quality of scientific evidence, it cannot be determined whether ENDS may help most smokers to quit or prevent them from doing so.

ABILITY OF ENDS/ENNDS TO INITIATE YOUTH IN NICOTINE USE AND SMOKING

18. WHO commissioned a review of the data on the prevalence and trends of ENDS/ENNDS use among people of 20 years of age or less⁶. The review identified a total of 27 studies that used probability sampling from very few countries. The age range of respondents varied across studies, as did the prevalence of ENDS/ENNDS use reported across jurisdictions. From 2013 to 2015, current use among non-smokers is around 2%, although in jurisdictions like Florida, USA and Poland it was 13% and 19%, respectively. Current use among smokers is around 17%, with Florida (44.8% in the 11–14 age range and 51.7% in the 15–18 age range) and Poland (57.4%) showing much higher prevalence^v.

19. Trend data of young people's current use of ENDS/ENNDS from probability sample surveys are only available from three countries: the USA, Poland and Italy. In Italy, current use of ENDS/ENNDS among smokers and non-smokers is very low and is not increasing. England presents a similar situation, although available trend data is not based on probability samples. The USA and Poland both show a rapid increase in the current use of ENDS/ENNDS. Use among non-smoking youth in Florida, USA and Poland has increased by a factor of five and eight respectively in three years, to reach a prevalence of 6.9% and 13% in these jurisdictions.

20. The trend data show that there are two groups of countries. In one, the prevalence of ENDS/ENNDS use is low and is not increasing significantly; in the other, which includes the largest market in the world (the USA), prevalence is rapidly increasing. There is considerable debate about whether in these countries the increase in ENDS/ENNDS use among young non-smokers is a precursor to smoking. Existing longitudinal studies^{64,65,66,67} indicate that ENDS/ENNDS use by minors who have never smoked at least doubles their chance of starting to smoke. It is not clear whether the association of ENDS/ENNDS use and smoking is because their use leads to smoking, or because young ENDS/ENNDS users and smokers share similar social and behavioural characteristics, rendering them susceptible to the use of nicotine.

^v Appendix 2 presents more details.

ENDS/ENNDS MARKETING

21. **Promotion:** There is insufficient research or surveillance on how and to what extent ENDS/ENNDS manufacturers are promoting their products in the main country markets⁶⁸. Existing data indicates that spending on ENDS/ENNDS advertising has been increasing since 2012^{69,70}; that marketing uses diverse channels - point-of-sale,⁷¹ audiovisual and print mass media and online⁷²; and that promotional approaches vary by type of manufacturer⁷³. An unquantified amount of advertising uses deceptive health claims and its targeting includes youth^{74,75,76,77,78} and incites rebellion against smoke-free policies⁷⁹. There are also concerns that some companies are using or might use ENDS/ENNDS advertising to promote smoking, advertently or unintentionally^{80,81,82}.

22. **Price:** The limited empirical research on the topic shows that:

- a. ENDS/ENNDS sales and prices have a strong inverse relation⁸³;
- b. ENDS/ENNDS and cigarettes are substitutes, with higher cigarette prices being associated with increased ENDS/ENNDS sales⁸⁴. Therefore, differential tax policies based on product type could lead to substitution between different types of ENDS/ENNDS and between ENDS/ENNDS and cigarettes⁸⁵;
- c. Existing initial costs for a rechargeable ENDS/ENNDS devices and costs of disposable ENDS/ENNDS are generally higher than those of cigarettes⁸⁶.

23. **Product characteristics:** Flavour is one of several significant product appeal factors that influences people's willingness to try ENDS. Certain flavours, such as fruit and confectionary or candy-like aromas, appeal to children, younger never-smokers and young ENDS/ENNDS beginners^{87,88,89,90} and may therefore play a role in motivating experimentation among them. In 2009, one company declared that they would halt flavour sales to discourage underage use⁹¹ although years later they reversed their decision. Flavours also seem to play a role among adults and experienced ENDS/ENNDS users in helping migration away from tobacco⁹². Flavoured ENDS/ENNDS may be, therefore, one of several product features that appeal to taste predilections, while also suggesting a level of safety and building user image.

24. **Product placement:** Internet sales, as opposed to those in retail stores, accounted for one-third of the worldwide market in 2014. In three regions - Asia Pacific, Australasia and Latin America - Internet sales accounted for the largest share of the market (70%, 85% and 94%, respectively).

COMMERCIAL INTERESTS

25. Initially, the growth of the ENDS/ENNDS market was driven by companies that were independent from traditional tobacco transnational companies (TTCs). However, TTCs are rapidly increasing their share of what is so far a generally unregulated market. Some^{93,94} argue that recently approved regulations in the USA and the European Union - the main ENDS/ENNDS markets in size - will force a market concentration as a result of the costs of bringing regulated devices to market and that this will allow TTCs to increase their market dominance.

26. The engagement of TTCs in the marketing of ENDS/ENNDS is a major threat to tobacco control. There are concerns that TTCs are marketing ENDS/ENNDS in order to:

- a. minimize the threat to tobacco sales by promoting ENDS as a complement rather than an alternative to tobacco, or controlling technological innovations that would prevent improvements in their efficacy as an aid to cessation;
- b. promote smoking through ENDS/ENNDS advertising, and promotion to adults and children;
- c. assert potential benefits of ENDS/ENNDS - and, in the near future, nicotine inhaler technology - as an excuse to engage with and influence policymakers, scientists and advocates in tobacco control with a view to undermining the WHO FCTC, while at the same time building credibility in corporate social responsibility initiatives.

27. A growing concern is the extent to which research on the topic has links to commercial and other vested interests of the ENDS/ENNDS industry, including the tobacco industry, and its allies. In a review⁵ of 105 studies analysing the composition of liquids and emissions, 30% had authors that had received funding from ENDS/ENNDS interests - including the tobacco industry^{vi}.

REGULATORY OPTIONS

28. The following is a non-exhaustive list of options that Parties might consider in accordance with their national law, in order to achieve the ENDS/ENNDS objectives set out in the COP 6 decision on ENDS/ENNDS.

29. *Objective: prevent the initiation of ENDS/ENNDS by non-smokers and youth with special attention to vulnerable groups.* Although the debate about whether the use of ENDS/ENNDS is a gateway to smoking is unresolved, preventing this eventuality requires making the initiation and persistence of smoking as difficult as possible. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options:

- a. Banning the sale and distribution of ENDS/ENNDS to minors;
- b. Banning the possession of ENDS/ENNDS by minors;
- c. Banning or restricting advertising, promotion and sponsorship of ENDS/ENNDS (see FCTC/COP/6/10 Rev.1);
- d. Taxing ENDS/ENNDS at a level that makes the devices and e-liquids unaffordable to minors in order to deter its use in this age group^{vii}. In parallel, combustible tobacco products should be taxed at a higher level than ENDS/ENNDS to deter initiation and reduce regression to smoking;
- e. Banning or restricting the use of flavours that appeal to minors;
- f. Regulating places, density and channels of sales; and
- g. Taking measures to combat illicit trade in ENDS/ENNDS.

30. *Objective: minimize as far as possible potential health risks to ENDS/ENNDS users and protect non-users from exposure to their emissions.*

- a. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options to minimize health risks to users:
 - i. Testing heated and inhaled flavourants used in the e-liquids for safety, and banning or restricting the amount of those found to be of serious toxicological concern such as diacetyl, acetyl propionyl, cinnamaldehydes or benzaldehyde;
 - ii. Requiring the use of ingredients that are not a risk to health and are, when allowed, of the highest purity;
 - iii. Regulating electrical and fire safety standards of ENDS/ENNDS devices;
 - iv. Regulating the need for manufacturers to disclose product content to government;
 - v. Regulating appropriate labelling of devices and e-liquids;
 - vi. Requiring manufacturers to monitor and report adverse effects; and
 - vii. Providing for the removal of products that do not comply with regulations.

^{vi} See Appendix 3

^{vii} If ENDS/ENNDS are regulated as prescribed medicinal products and regulations are well-enforced, the current taxation policy for these products should be applied.

- b. Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options to minimize health risks to non-users:
 - i. Prohibiting by law the use of ENDS/ENNDS in indoor spaces or at least where smoking is not permitted^{viii};
 - ii. Requiring health warnings about potential health risks deriving from their use. Health warnings may additionally inform the public about the addictive nature of nicotine in ENDS; and
 - iii. Reducing the risk of accidental acute nicotine intoxication by a) requiring tamper-evident/child resistant packaging for e-liquids and leak-proof containers for devices and e-liquids and b) limiting the nicotine concentration and total nicotine amount in devices and e-liquids.

31. *Objective: prevention of unproven health claims being made about ENDS/ENNDS.* Parties that have not banned the importation, sale, and distribution of ENDS/ENNDS may consider the following options:

- a. Prohibiting implicit or explicit claims about the effectiveness of ENDS/ENNDS as smoking cessation aids unless a specialized governmental agency has approved them;
- b. Prohibiting implicit or explicit claims that ENDS/ENNDS are innocuous or that ENDS are not addictive; and
- c. Prohibiting implicit or explicit claims about the comparative safety or addictiveness of ENDS/ENNDS with respect to any product unless these have been approved by a specialized governmental agency.

32. *Objective: protect tobacco control activities from all commercial and other vested interests related to ENDS/ENNDS, including interests of the tobacco industry.* Parties, including those that have banned the importation, sale, and distribution of ENDS/ENNDS, may consider the following options:

- a. Raising awareness about potential industry interference with Parties' tobacco control policies;
- b. Establishing measures to limit interactions with the industry and to ensure transparency in those interactions that do take place;
- c. Rejecting partnerships with the industry;
- d. Taking measures to prevent conflicts of interest for government officials and employees;
- e. Requiring that information provided by the industry be transparent and accurate;
- f. Banning activities described as "socially responsible" by the industry, including but not limited to activities described as "corporate social responsibility";
- g. Refusing to give preferential treatment to industry; and
- h. Treating State-owned industry in the same way as any other industry.

ACTION BY THE CONFERENCE OF THE PARTIES

33. The COP is invited to note this report and provide further guidance.

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^{viii} See Appendix 4.

REFERENCES

- ¹ FCTC/COP/6/9
- ² http://www.who.int/tobacco/industry/product_regulation/tobreg/en/
- ³ Fernandez, E., et al, Institut Català d'Oncologia, Exposure to Aerosols from Smoking-proxy Electronic Inhaling Systems: a Systematic Review, unpublished report, (2016) Fernandez
- ⁴ El Dib, R., et al, Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: A systematic review and meta-analysis, unpublished report (2016)
- ⁵ Pisinger, C., Research Centre for Prevention and Health, A systematic review of health effects of electronic cigarettes, unpublished report (2015)
- ⁶ Yoong, et. Al., Prevalence of Smoking-proxy Electronic Inhaling Systems (SEIS) use and its association with tobacco initiation in youth, unpublished report (2016)
- ⁷ Based on Euromonitor's 2015 data
- ⁸ Mickle T. E-Cigarette Sales Rapidly Lose Steam [Internet]. WSJ. 2016 [cited 2 June 2016]. Available from: <http://www.wsj.com/articles/e-cig-sales-rapidly-lose-steam-1447798921>
- ⁹ Japan Tobacco International. JTI acquires "Ploom" Intellectual Property Rights from Ploom, Inc. [Internet]. Jti.com. 2015 [cited 2 June 2016]. Available from: <http://www.jti.com/media/news-releases/jti-acquires-ploom-intellectual-property-rights-ploom-inc/>
- ¹⁰ Philip Morris International. A New Era Begins in Japan: Revolutionary Tobacco Heating Technology 'iQOS' to be Rolled Out Nationwide [Internet]. 2015 [cited 2 June 2016]. Available from: http://www.pmi.com/ja_jp/media_center/press_releases/Documents/20150818iQOS_E.pdf
- ¹¹ Spencer B. The iFuse 'hybrid' cigarette combines e-cig technology with tobacco [Internet]. Mail Online. 2015 [cited 3 June 2016]. Available from: <http://www.dailymail.co.uk/sciencetech/article-3330238/The-iFuse-hybrid-cigarette-combines-e-cig-technology-tobacco-improve-flavour-vapour.html>
- ¹² Moyses C, Hearn A, Redfern A. Evaluation of a Novel Nicotine Inhaler Device: Part 1--Arterial and Venous Pharmacokinetics. *Nicotine & Tobacco Research*. 2014;17(1):18-25.
- ¹³ Moyses C, Hearn A, Redfern A. Evaluation of a Novel Nicotine Inhaler Device: Part 2--Effect on Craving and Smoking Urges. *Nicotine & Tobacco Research*. 2014;17(1):26-33.
- ¹⁴ Rose J, Turner J, Murugesan T, Behm F, Laugesen M. Pulmonary delivery of nicotine pyruvate: Sensory and pharmacokinetic characteristics. *Experimental and Clinical Psychopharmacology*. 2010;18(5):385-394.
- ¹⁵ Visser W, Geraets L, Klerx W, Hernandez L, Stephens E, Croes E et al. The health risks of using e-cigarettes. [Internet]. Bilthoven The Netherlands: National Institute for Public Health and the Environment; 2015. Available from: <http://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf>
- ¹⁶ Goniewicz M, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco Control*. 2013;23(2):133-139.
- ¹⁷ U.S. Department of Health and Human Services. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Rockville, MD: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2014.
- ¹⁸ Kutlu MGould T. Nicotine modulation of fear memories and anxiety: Implications for learning and anxiety disorders. *Biochemical Pharmacology*. 2015;97(4):498-511.
- ¹⁹ Yuan M, Cross S, Loughlin S, Leslie F. Nicotine and the adolescent brain. *J Physiol*. 2015;593(16):3397-3412.
- ²⁰ Hall F, Der-Avakian A, Gould T, Markou A, Shoaib M, Young J. Negative affective states and cognitive impairments in nicotine dependence. *Neuroscience & Biobehavioral Reviews*. 2015;58:168-185.
- ²¹ Zhu S, Sun J, Bonnevie E, Cummins S, Gamst A, Yin L et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco Control*. 2014;23(suppl 3):iii3-iii9.
- ²² Barrington-Trimis J, Samet J, McConnell R. Flavorings in Electronic Cigarettes. *JAMA*. 2014;312(23):2493.
- ²³ Kreiss K, Gomaa A, Kullman G, Fedan K, Simoes E, Enright P. Clinical Bronchiolitis Obliterans in Workers at a Microwave-Popcorn Plant. *New England Journal of Medicine*. 2002;347(5):330-338.
- ²⁴ Harber P, Saechao K, Boomus C. Diacetyl-Induced Lung Disease. *Toxicological Reviews*. 2006;25(4):261-272.
- ²⁵ Behar R, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicology in Vitro*. 2014;28(2):198-208.
- ²⁶ van Assendelft A. Adverse drug reactions checklist. *BMJ*. 1987;294(6571):576-577.
- ²⁷ Saint DM, Vanillin-triggered migraine. *Food and Chemical Toxicology*. 1997;35(5):527-528.
- ²⁸ Tierney P, Karpinski C, Brown J, Luo W, Pankow J. Flavour chemicals in electronic cigarette fluids. *Tobacco Control*. 2015;25(e1):e10-e15.

- ²⁹ Lerner C, Sundar I, Yao H, Gerloff J, Ossip D, McIntosh S et al. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. *PLOS ONE*. 2015;10(2):e0116732.
- ³⁰ Cervellati F, Muresan X, Sticozzi C, Gambari R, Montagner G, Forman H et al. Comparative effects between electronic and cigarette smoke in human keratinocytes and epithelial lung cells. *Toxicology in Vitro*. 2014;28(5):999-1005.
- ³¹ Wu Q, Jiang D, Minor M, Chu H. Electronic Cigarette Liquid Increases Inflammation and Virus Infection in Primary Human Airway Epithelial Cells. *PLoS ONE*. 2014;9(9):e108342.
- ³² Bahl V, Lin S, Xu N, Davis B, Wang Y, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reproductive Toxicology*. 2012;34(4):529-537.
- ³³ Britton J, Arnott D, McNeill A, Hopkinson N. Nicotine without smoke—putting electronic cigarettes in context. *BMJ*. 2016;:i1745.
- ³⁴ Public Health England. E-cigarettes: a new foundation for evidence-based policy and practice [Internet]. Public Health England. 2015 [cited 22 June 2016]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/454517/E-cigarettes_a_firm_foundation_for_evidence_based_policy_and_practice.pdf
- ³⁵ McNeill A, Brose L, Calder R, Hitchman S, Hajek P, McRobbie H. E-cigarettes: an evidence update A report commissioned by Public Health England [Internet]. Public Health England. 2015 [cited 22 June 2016]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/E-cigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf
- ³⁶ McNeill A, Brose L, Calder R, Hitchman S, Hajek P, McRobbie H. Underpinning evidence for the estimate that e-cigarette use is around 95% safer than smoking: authors' note [Internet]. Public Health England. 2015 [cited 22 June 2016]. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/456704/McNeill-Hajek_report_authors_note_on_evidence_for_95_estimate.pdf
- ³⁷ Levy D, Borland R, Villanti A, Niaura R, Yuan Z, Zhang Y et al. The Application of a Decision-Theoretic Model to Estimate the Public Health Impact of Vaporized Nicotine Product Initiation in the United States. *Nicotine & Tobacco Research*. 2016;:ntw158.
- ³⁸ Kalkhoran S, Glantz S. Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom. *JAMA Internal Medicine*. 2015;175(10):1671.
- ³⁹ Combes RD, Balls M. On the safety of e-cigarettes: "I can resist anything except temptation". *Alternatives to Laboratory Animals*. 2015;43(6):417-425.015;43(6):417-425.
- ⁴⁰ British American Tobacco. A new framework for assessing Potentially Reduced Risk Tobacco and Nicotine products [Internet]. *Bat-science.com*. 2015 [cited 19 July 2016]. Available from: http://www.bat-science.com/groupms/sites/BAT_9GVJXS.nsf/vwPagesWebLive/DOA3XF63?opendocument#
- ⁴¹ Philip Morris International. Reduced-Risk Product Development [Internet]. *Pmi.com*. [cited 19 July 2016]. Available from: http://www.pmi.com/eng/research_and_development/Pages/reduced_risk_product_development.aspx#
- ⁴² Hess I, Lachireddy K, Capon A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. *Public Health Research & Practice*. 2016;26(2).
- ⁴³ Bertholon J, Becquemin M, Roy M, Roy F, Ledur D, Annesi Maesano I et al. Comparaison de l'aérosol de la cigarette électronique à celui des cigarettes ordinaires et de la chicha. *Revue des Maladies Respiratoires*. 2013;30(9):752-757.
- ⁴⁴ Ballbè M, Martínez-Sánchez JM, Sureda X, Fu M, Pérez-Ortuño R, Pascual JA, et al. Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environ Res*. 2014;135:76–80.
- ⁴⁵ Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. *Int J Environ Res Public Health*. 2014;11:11177–91.
- ⁴⁶ Ruprecht AA, De Marco C, Pozzi P, Munarini E, Mazza R, Angellotti G, et al. Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. *Tumori*. 2014;100:24–7.
- ⁴⁷ Saffari A, Daher N, Ruprecht A, De Marco C, Pozzi P, Boffi R, et al. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environ Sci Process Impacts*. 2014;16:2259–67.
- ⁴⁸ Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air*. 2013;23:25–31. *Environ Sci Process Impacts*. 2014;16:2259–67.
- ⁴⁹ Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res*. 2014;16:655–62.
- ⁵⁰ Marco E, Grimalt JO. A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers. *J Chromatogr A*. 2015;1410:51–9.
- ⁵¹ Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. *Int J Environ Res Public Health*. 2014;11:11177–91.
- ⁵² Saffari A, Daher N, Ruprecht A, De Marco C, Pozzi P, Boffi R, et al. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environ Sci Process Impacts*. 2014;16:2259–67.

- ⁵³ Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, et al. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health*. 2014;217:628–37.
- Vargas Trassierra C, Cardellini F, Buonanno G, De Felice P. On the interaction between radon progeny and particles generated by electronic and traditional cigarettes. *Atmos Environ*. 2015;106:442–50.
- ⁵⁴ O’Connell G, Colard S, Cahours X, Pritchard J. An Assessment of Indoor Air Quality before, during and after Unrestricted Use of E-Cigarettes in a Small Room. *Int J Environ Res Public Health*. 2015;12:4889–907.
- ⁵⁵ Vargas Trassierra C, Cardellini F, Buonanno G, De Felice P. On the interaction between radon progeny and particles generated by electronic and traditional cigarettes. *Atmos Environ*. 2015;106:442–50.
- ⁵⁶ Royal College of Physicians. Nicotine without smoke: Tobacco harm reduction [Internet]. Rcpplondon.ac.uk. 2016 [cited 31 July 2016]. Available from: <https://www.rcplondon.ac.uk/file/3563/download?token=uV0R0Twz>
- ⁵⁷ Public Health England. Use of e-cigarettes in public places and workplaces. London, England: Public Health England; 2016.
- ⁵⁸ Unger J. E-Cigarettes: Introducing New Complexities and Controversies to the Field of Nicotine and Tobacco Research. *Nicotine & Tobacco Research*. 2015;17(10):1185-1186.
- ⁵⁹ McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database of Systematic Reviews*. 2014.
- ⁶⁰ GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490-0.
- ⁶¹ Kalkhoran S, Glantz S. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *The Lancet Respiratory Medicine*. 2016;4(2):116-128.
- ⁶² Biener L, Hargraves J. A Longitudinal Study of Electronic Cigarette Use Among a Population-Based Sample of Adult Smokers: Association With Smoking Cessation and Motivation to Quit. *Nicotine & Tobacco Research*. 2014;17(2):127-133.
- ⁶³ Brose L, Hitchman S, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction*. 2015;110(7):1160-1168.
- ⁶⁴ Leventhal A, Strong D, Kirkpatrick M, Unger J, Sussman S, Riggs N et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA*. 2015;314(7):700.
- ⁶⁵ Primack B, Soneji S, Stoolmiller M, Fine M, Sargent J. Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. *JAMA Pediatrics*. 2015;169(11):1018.
- ⁶⁶ Wills T, Knight R, Sargent J, Gibbons F, Pagano I, Williams R. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. *Tobacco Control*. 2016;:tobaccocontrol-2015-052705.
- ⁶⁷ Barrington-Trimis J, Urman R, Berhane K, Unger J, Cruz T, Pentz M et al. E-Cigarettes and Future Cigarette Use. *Pediatrics*. 2016;.
- ⁶⁸ A sample collection of ENDS/ENNDS advertisement can be seen here: http://tobacco.stanford.edu/tobacco_main/ecigs.php
- ⁶⁹ Cantrell J, Emelle B, Ganz O, Hair E, Vallone D. Rapid increase in e-cigarette advertising spending as Altria’s MarkTen enters the marketplace. *Tobacco Control*. 2015;25(e1):e16-e18.
- ⁷⁰ Kornfield R, Huang J, Vera L, Emery S. Rapidly increasing promotional expenditures for e-cigarettes. *Tobacco Control*. 2014;24(2):110-111.
- ⁷¹ Ganz O, Cantrell J, Moon-Howard J, Aidala A, Kirchner T, Vallone D. Electronic cigarette advertising at the point-of-sale: a gap in tobacco control research. *Tobacco Control*. 2014;24(e1):e110-e112.
- ⁷² Huang J, Kornfield R, Szczycka G, Emery S. A cross-sectional examination of marketing of electronic cigarettes on Twitter. *Tobacco Control*. 2014;23(suppl 3):iii26-iii30.
- ⁷³ Seidenberg A, Jo C, Ribisl K. Differences in the design and sale of e-cigarettes by cigarette manufacturers and non-cigarette manufacturers in the USA: Table 1. *Tobacco Control*. 2015;25(e1):e3-e5.
- ⁷⁴ Grana R, Ling P. “Smoking Revolution”. *American Journal of Preventive Medicine*. 2014;46(4):395-403.
- ⁷⁵ Richardson A, Ganz O, Vallone D. Tobacco on the web: surveillance and characterisation of online tobacco and e-cigarette advertising. *Tobacco Control*. 2014;24(4):341-347.
- ⁷⁶ Cobb N, Brookover J, Cobb C. Forensic analysis of online marketing for electronic nicotine delivery systems. *Tobacco Control*. 2013;24(2):128-131.
- ⁷⁷ Singh T, Marynak K, Arrazola R, Cox S, Rolle I, King B. Vital Signs : Exposure to Electronic Cigarette Advertising Among Middle School and High School Students — United States, 2014. *MMWR Morbidity and Mortality Weekly Report*. 2016;64(52):1403-1408.
- ⁷⁸ Ramamurthi D, Fadadu R, Jackler R. Electronic cigarette marketers manipulate antitobacco advertisements to promote vaping. *Tobacco Control*. 2015;:tobaccocontrol-2015-052661.
- ⁷⁹ Rooke C, Amos A. News media representations of electronic cigarettes: an analysis of newspaper coverage in the UK and Scotland: Table 1. *Tobacco Control*. 2013;23(6):507-512.

-
- ⁸⁰ Andrade M, Hastings G, Angus K. Promotion of electronic cigarettes: tobacco marketing reinvented?. *BMJ*. 2013;347(dec20 1):f7473-f7473.
- ⁸¹ National Institute for Health and Care Excellence. Smoking: harm reduction | 3-Considerations | Guidance and guidelines | NICE [Internet]. *Nice.org.uk*. 2013 [cited 20 July 2016]. Available from: <https://www.nice.org.uk/guidance/ph45/chapter/3-Considerations>
- ⁸² Advertising Standards Authority. Ruling on Mirage Cigarettes Ltd - Advertising Standards Authority [Internet]. *Asa.org.uk*. 2015 [cited 20 July 2016]. Available from: https://www.asa.org.uk/Rulings/Adjudications/2015/4/Mirage-Cigarettes-Ltd/SHP_ADJ_292291.aspx#.V4-DZrjhDIU
- ⁸³ Huang J, Tauras J, Chaloupka F. The impact of price and tobacco control policies on the demand for electronic nicotine delivery systems. *Tobacco Control*. 2014;23(suppl 3):iii41-iii47.
- ⁸⁴ Stoklosa M, Drope J, Chaloupka F. Prices and E-Cigarette Demand: Evidence From the European Union. *Nicotine & Tobacco Research*. 2016;:ntw109.
- ⁸⁵ Chaloupka F, Sweanor D, Warner K. Differential Taxes for Differential Risks — Toward Reduced Harm from Nicotine-Yielding Products. *New England Journal of Medicine*. 2015;373(7):594-597.
- ⁸⁶ Liber A, Drope J, Stoklosa M. Combustible cigarettes cost less to use than e-cigarettes: global evidence and tax policy implications. *Tobacco Control*. 2016;:tobaccocontrol-2015-052874.
- ⁸⁷ Czoli C, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: results from a discrete choice experiment. *Tobacco Control*. 2015;25(e1):e30-e36.
- ⁸⁸ Ford A, MacKintosh A, Bauld L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. *International Journal of Public Health*. 2015;61(2):215-224.
- ⁸⁹ Ambrose B, Day H, Rostron B, Conway K, Borek N, Hyland A et al. Flavored Tobacco Product Use Among US Youth Aged 12-17 Years, 2013-2014. *JAMA*. 2015;314(17):1871.
- ⁹⁰ Vasiljevic M, Petrescu D, Marteau T. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. *Tobacco Control*. 2016;:tobaccocontrol-2015-052593.
- ⁹¹ Business Wire. NJOY to Discontinue Flavors, Takes Additional Steps to Prevent Underage Electronic Cigarette Use [Internet]. *Reuters*. 2016 [cited 10 May 2016]. Available from: <http://www.reuters.com/article/idUS219183+10-Dec-2009+BW20091210>
- ⁹² Farsalinos K, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey. *International Journal of Environmental Research and Public Health*. 2013;10(12):7272-7282.
- ⁹³ Burrus T. Why Big Tobacco Loves the New FDA E-Cig Regulations [Internet]. *Cato Institute*. 2016 [cited 31 July 2016]. Available from: <http://www.cato.org/blog/why-big-tobacco-loves-new-fda-e-cig-regulations>
- ⁹⁴ Snowdon C. E-cigarettes and Article 20 of the Tobacco Products Directive [Internet]. *Epicenter*. [cited 31 July 2016]. Available from: <http://www.epicenternetwork.eu/wp-content/uploads/2015/09/EPICENTER-Briefing-E-cigarettes-and-Article-20-14th-September-2015.pdf>