Heated tobacco products - No smoke without fire?

By Marine Faure, Charlotta Pisinger, European Respiratory Society

Back in the 1960s, when smoking was more popular, cigarettes were used as fashion accessories and models, writers and other media personalities would not hesitate to pose either holding or smoking a cigarette. Yet, this was also the period when public concerns about smoking and health began to rise. As a result, in the 1980's tobacco companies developed a brand-new type of cigarettes promoted as "light" and "low-tar". Tobacco advertising created the perception that a healthier cigarette was available on the market[1] and very quickly, many smokers identified the so-called 'light' cigarette as a safe alternative to smoking[1]. Studies have since shown that the risk of serious health effects was not actually lower for smokers of "light" and "low-tar" cigarettes and indeed sometimes increased [2] [3]. More recently, the continuing global decline in tobacco consumption has led the tobacco industry to introduce and massively advertise new "heated tobacco products" that they claim to be significantly less harmful that traditional cigarettes. Given the history of tobacco companies using reduced exposure to mislead smokers who want to quit, it is important to evaluate, in the light of the existing scientific evidence, what really are heated tobacco products and their impact on consumers' health.

What are heated tobacco products?

Heated tobacco is a new nicotine delivery system, commonly referred to as "Heat-not-Burn" by the tobacco industry. Heated tobacco products consist of a small tobacco stick that is heated electronically, rather than burned. The tobacco industry is actively pursuing the market with sales on the rise of products such as 'iQOS' and 'glo'.

Tobacco industry research claims a 90-95% reduction in harm

According to a tobacco industry press release, the main ingredient in heated tobacco products is water, whereas the main ingredient in conventional cigarettes is tar. The tobacco industry claims that there is a 90-95% reduction in harmful and potentially harmful substances and toxicity[4].

Not the full picture: digging deeper into tobacco industry research

Tobacco companies have not informed the public that their studies on emissions from heated tobacco found high concentrations of e.g. particulate matter, tar, acetaldehyde (a carcinogen), acrylamide (a potential carcinogen), an acrolein metabolite (toxic and irritant) [5-9] and formaldehyde (a potential carcinogen) [10] [11]. Independent researchers have investigated tobacco industry data and point out that heated tobacco products emit significantly higher levels of several substances that are not recognised as harmful or potentially harmful by the US Food and Drug Administration (FDA) compared with combustible cigarette smoke. Levels of twenty two harmful or potentially harmful substances were more than 200% higher and seven were more than 1000% higher than in reference cigarette smoke [12].Further, human studies show that there is no statistically detectable difference between users of heated tobacco and conventional cigarette for 23 of the 24 biomarkers of potential harm [13]. Both animal and human studies performed by the tobacco industry also show there is no evidence of improvement in pulmonary function or inflammation in smokers who switched to heated tobacco [14] and there is possible hepatotoxicity of heated tobacco [15].

Independent research: a substantially higher risk than claimed by the tobacco industry

Historically, doubt has been cast on the independence of studies carried out by the tobacco industry or researchers funded by

them[16-20]. Former employees and contractors have detailed irregularities in the clinical experiments on heated tobacco products performed by the industry [21].

Independent research shows that heated tobacco products emit substantial levels of carcinogenic tobacco specific nitrosamines [22] [23] as well as toxic and irritant substances and potential carcinogens [24]. Nicotine and tar levels have been found to be almost identical to a conventional cigarette [25], the potentially carcinogenic substance acenaphthene is found to be almost 3 times higher than in conventional cigarettes [24], and release of formaldehyde cyanohydrin takes place, which is of great concern as it is highly toxic at very low concentrations [26]. In-vitro studies found that emissions for heated tobacco cause damage to human bronchial epithelial cells [27], have the potential to increase oxidative stress and inflammation, infections and airway remodeling and initiate epithelial mesenchymal transition-related changes in the airways [28]. Experimental animal studies found that exposure to heated tobacco led to decreased blood vessel function comparable to that induced by cigarette smoke [29] and impaired arterial flow-mediated dilation, a measure of vascular endothelial function in a manner very similar to tobacco smoke [30]. In addition, a study found that users of heated tobacco may be forced to smoke more quickly which could lead to an increase in intake of carbonyls (potentially carcinogenic) and nicotine, inducing a high level of nicotine dependence [26].

What does ERS recommend?

Even though heated tobacco products may perhaps be less harmful for smokers they nevertheless remain both harmful and highly addictive, and there may be a risk that smokers will switch to heated tobacco products instead of stopping smoking. ERS cannot recommend any product which damages the lungs and human health.

Why does ERS make this recommendation?

It is tempting to recommend to smokers to switch to heated tobacco products without considering all of the consequences. Experiences with filter cigarettes and light cigarettes have shown that 'safer products' undermine smokers' wish to stop smoking, while not improving smokers' health [3]. Quoting the tobacco industry on 'safer products': *"Quitters may be discouraged from quitting, or at least kept in the market longer …"*[1]. We must remember that two to three out of four smokers want to quit [31] and almost all smokers regret starting to smoke [32] [33]. Also, many smokers want to quit because they want to regain control of their life [34] [35], and get cured of their nicotine dependency – this will not happen if they switch to heated tobacco products. A majority of smokers want to quit, and there is not a 'hardening' of smokers[36] – on contrary there are fewer hard core smokers [37] and they report being less dependent [38] . We have no evidence that heated tobacco products are efficient as smoking cessation aid. Dual use is very frequent for other harm reduction products as e-cigarettes (approx. 70-80%)[39] [40] and snuff/snus (>40%)[41], and dual use of heated tobacco cigarettes combined with conventional cigarettes cannot be ruled out. Finally, ex-smokers and never-smokers might be tempted to start using this 'harmless' product and a re-normalisation of smoking in public might occur [42]. Four studies show that heated tobacco is used by non-smokers in up to 45% of cases [43].

The European Commission underlines that "with regard to the sale, presentation and manufacturing of these products within the European Union, the relevant provisions of the Tobacco Products Directive apply and should be enforced. This includes a ban on misleading elements foreseen by Article 13 and notably any suggestions that a particular tobacco product is less harmful than another [44].

EU Member states are currently assessing the toxicity of these products. For example, there is concern in the UK" over the potential for non-smokers including children and young people, who would not otherwise start to smoke cigarettes, to start using these products, as they are not without risk. There has also been concern over whether use of these products would lead people to take up smoking cigarettes" [45].

These concerns are also being aired outside Europe. An expert scientific panel has advised the US FDA to vote against the tobacco industry's claim that heated tobacco products cut the risk of tobacco-related diseases and that a heated tobacco product is less risky than continuing to smoke cigarettes [46] .

At the last opening of the Conference of Parties (COP) to the WHO Framework Convention on Tobacco Control, Dr Vera da Luiza Costa, head of the WHO FCTC secretariat, raised her concerns regarding new emerging products and recommended parties to the Convention to " expedite implementation of article 5.3 Guidelines and ensure that its applicable to all commercial and vested interests of the tobacco industry, including addressing unproven claims of harm reduction" [47].

Conclusion

Based on current science-based evidence, we can conclude that heated tobacco products are not harmless, as claimed by the tobacco industry. Even if they turn out to be less harmful than conventional cigarettes, they might have a negative impact on public health. These products were introduced for the same reasons as "low tar" and "light" cigarettes: to prevent smokers from quitting and attract non-smokers. Just like regular tobacco smoking and smokeless tobacco, they remain addictive and carcinogenic to humans[48 49]. We should not allow debate around these new tobacco products to distract us from the main job at hand – promoting regulatory measures that we know are effective at reducing smoking, continue to support those who wish to stop smoking and tell smokers that the safest tobacco product on the market is the one they will never smoke.

References

1. Cunningham R. Smoke and mirrors : the Canadian tobacco war. Note on: Creative Research group, Project Viking, Volume 11: An Attitudinal Model of Smoking, 1986, February- March, prepared for Imperial Tobacco Limited (Canada). International Development Reasearch Center1996.

2. Song MA, Benowitz NL, Berman M, et al. Cigarette Filter Ventilation and its Relationship to Increasing Rates of Lung Adenocarcinoma. *Journal of the National Cancer Institute* 2017;109(12) doi: 10.1093/jnci/djx075 [published Online First: 2017/05/20]

3. Harris JE, Thun MJ, Mondul AM, et al. Cigarette tar yields in relation to mortality from lung cancer in the cancer prevention study II prospective cohort, 1982-8. *Bmj* 2004;328(7431):72. doi: 10.1136/bmj.37936.585382.44 [published Online First: 2004/01/13]

4. Gilcrist M. Heat-not-burn products. Scientific Assessment of Risk Reduction. https://www.pmiscience.com/system/files/publications/presentation_moira_gilchrist_gtnf_2015a.pdf. In: International PM, ed. Global Tobacco and Nicotine Forum 2015 Annual Meeting Sept 17, 2015

5. Szostak J, Boue S, Talikka M, et al. Aerosol from Tobacco Heating System 2.2 has reduced impact on mouse heart gene expression compared with cigarette smoke. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association* 2017;101:157-67. doi: 10.1016/j.fct.2017.01.013 [published Online First: 2017/01/24]

6. Tricker AR, Stewart AJ, Leroy CM, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 3: Eight-day randomized clinical trial in the UK. *RegulToxicolPharmacol* 2012;64(2 Suppl):S35-S44.

7. Tricker AR, Jang IJ, Martin LC, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 4: Eight-day randomized clinical trial in Korea. *RegulToxicolPharmacol* 2012;64(2 Suppl):S45-S53.

8. Tricker AR, Kanada S, Takada K, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 5: 8-Day randomized clinical trial in Japan. *RegulToxicolPharmacol* 2012;64(2 Suppl):S54-S63.

9. Tricker AR, Kanada S, Takada K, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 6: 6-Day

randomized clinical trial of a menthol cigarette in Japan. *RegulToxicolPharmacol* 2012;64(2 Suppl):S64-S73.

10. Urban HJ, Tricker AR, Leyden DE, et al. Reduced exposure evaluation of an Electrically Heated Cigarette Smoking System. Part 8: Nicotine bridging--estimating smoke constituent exposure by their relationships to both nicotine levels in mainstream cigarette smoke and in smokers. *RegulToxicolPharmacol* 2012;64(2 Suppl):S85-S97.

11. Stabbert R, Voncken P, Rustemeier K, et al. Toxicological evaluation of an electrically heated cigarette. Part 2: Chemical composition of mainstream smoke. *JApplToxicol* 2003;23(5):329-39.

12. St Helen G, Jacob Iii P, Nardone N, et al. IQOS: examination of Philip Morris International's claim of reduced exposure. *Tob Control* 2018;27(Suppl 1):s30-s36. doi: 10.1136/tobaccocontrol-2018-054321 [published Online First: 2018/08/31]

13. Glantz SA. PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes. *Tob Control* 2018 doi: 10.1136/tobaccocontrol-2018-054413 [published Online First: 2018/08/23]

14. Moazed F, Chun L, Matthay MA, et al. Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. *Tob Control* 2018;27(Suppl 1):s20-s25. doi: 10.1136/tobaccocontrol-2018-054296 [published Online First: 2018/08/31]

15. Chun L, Moazed F, Matthay M, et al. Possible hepatotoxicity of IQOS. *Tob Control* 2018;27(Suppl 1):s39-s40. doi: 10.1136/tobaccocontrol-2018-054320 [published Online First: 2018/08/23]
16. Proctor RN. Golden Holocaust. Origins of the Cigarette Catastrophe and the Case for Abolition. Berkeley and Los Angeles, California: University of California Press 2011.

17. Barnes DE, Hanauer P, Slade J, et al. Environmental tobacco smoke. The Brown and Williamson documents. *JAMA* 1995;274(3):248-53.

18. Hong MK, Bero LA. How the tobacco industry responded to an influential study of the health effects of secondhand smoke. *BMJ* 2002;325(7377):1413-16.

19. Barnes DE, Bero LA. Industry-funded research and conflict of interest: an analysis of research sponsored by the tobacco industry through the Center for Indoor Air Research. *JHealth PolitPolicy Law* 1996;21(3):515-42.

20. Barnes DE, Bero LA. Why review articles on the health effects of passive smoking reach different conclusions. *JAMA* 1998;279(19):1566-70.

21. Reuters Investigates. The Philip Morris files. https://www.reuters.com/investigates/special-report/tobacco-iqos-science/ 2017 [

22. Leigh NJ, Palumbo MN, Marino AM, et al. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tob Control* 2018;27(Suppl 1):s37-s38. doi: 10.1136/tobaccocontrol-2018-054318 [published Online First: 2018/09/23]

23. Bekki K, Inaba Y, Uchiyama S, et al. Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. *Journal of UOEH* 2017;39(3):201-07. doi: 10.7888/juoeh.39.201 [published Online First: 2017/09/15]

24. Auer R, Concha-Lozano N, Jacot-Sadowski I, et al. Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. *JAMA internal medicine* 2017;177(7):1050-52. doi: 10.1001/jamainternmed.2017.1419 [published Online First: 2017/05/23]

25. Li X, Luo Y, Jiang X, et al. Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. *Nicotine Tob Res* 2018 doi: 10.1093/ntr/nty005 [published Online First: 2018/01/11]

26. Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tob Control* 2018 doi: 10.1136/tobaccocontrol-2017-054104 [published Online First: 2018/03/15]

27. Leigh NJ, Tran PL, O'Connor RJ, et al. Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. *Tob Control* 2018;27(Suppl 1):s26-s29. doi: 10.1136/tobaccocontrol-2018-054317 [published Online First: 2018/09/07]

28. Sohal S, Eapen M, Naidu V, et al. IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. *ERJ Open Res* 2019; 5(00159-2018)

29. Nabavizadeh P, Liu J, Ibrahim S, et al. Poster presentation: Inhalation of Heat-Not-Burn Tobacco Aerosol Impairs Vascular Endothelial Function: Center for Tobacco Control Research and Education, 2017.

30. Nabavizadeh P, Liu J, Havel CM, et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tob Control* 2018 doi: 10.1136/tobaccocontrol-2018-054325 [published Online First: 2018/09/13]

31. Rosendahl Jensen H, Davidsen M, Ekholm M, et al. Danskernes Sundhed – Den Nationale Sundhedsprofil 2017. (National Health Survey 2017). www.sst.dk. Sundhedsstyrelsen, Islands Brygge 67, 2300 København S: Danish National Board of Health, 2018.

32. Sansone N, Fong GT, Lee WB, et al. Comparing the Experience of Regret and Its Predictors Among Smokers in Four Asian Countries: Findings From the ITC Surveys in Thailand, South Korea, Malaysia, and China. *NicotineTobRes* 2013;15(10):1663-72.

33. Fong GT, Hammond D, Laux FL, et al. The near-universal experience of regret among smokers in four countries: findings from the International Tobacco Control Policy Evaluation Survey. *NicotineTobRes* 2004;6 Suppl 3:S341-S51.

34. McCaul KD, Hockemeyer JR, Johnson RJ, et al. Motivation to quit using cigarettes: a review. *Addict Behav* 2006;31(1):42-56. doi: 10.1016/j.addbeh.2005.04.004 [published Online First: 2005/05/27]

35. Ahluwalia JS, McNagny SE, Clark WS. Smoking cessation among inner-city African Americans using the nicotine transdermal patch [see comments]. *J GenIntern Med* 1998;13(1):1-8.

36. Edwards R, Tu D, Newcombe R, et al. Achieving the tobacco endgame: evidence on the hardening hypothesis from repeated cross-sectional studies in New Zealand 2008-2014. *Tob Control* 2017;26(4):399-405. doi: 10.1136/tobaccocontrol-2015-052860 [published Online First: 2016/07/07]

37. Eriksen M, Mackay J, Ross H. The Tobacco Atlas: American Cancer Society. 250 Williams Street. Atlanta, Georgia, 30303 USA 2012.

38. Bommel, J, Nagelhout GE, Kleinjan M, et al. Prevalence of hardcore smoking in the Netherlands between 2001 and 2012: a test of the hardening hypothesis. *BMCPublic Health* 2016;16

39. Reid JL, Rynard VL, Czoli CD, et al. Who is using e-cigarettes in Canada? Nationally representative data on the prevalence of e-cigarette use among Canadians. *PrevMed* 2015;81:180-83.

40. Christensen T, Welsh E, Faseru B. Profile of e-cigarette use and its relationship with cigarette quit attempts and abstinence in Kansas adults. *Prev Med* 2014;69:90-4. doi: 10.1016/j.ypmed.2014.09.005 [published Online First: 2014/09/18]

41. Lund I, Scheffels J. Adolescent tobacco use practices and user profiles in a mature Swedish moist snuff (snus) market: Results from a school-based cross-sectional study. *Scand J Public Health* 2016 doi: 10.1177/1403494816656093 [published Online First: 2016/06/25]

42. Wells Fargo: Probability Of PM/MO Combo Now Higher - iQOS Remains A Key Catalyst & Is Driving Transformative Growth.
https://www.tma.org/article/2017/wells-fargo-probability-pmmo-combo-now-higher-iqos-remains-key-catalyst-driving: Wells Fargo Securities, LLC, 18. 12. 2016.

43. Dautzenberg B, Dautzenberg MD. [Systematic analysis of the scientific literature on heated tobacco]. *Revue des maladies respiratoires* 2019;36(1):82-103. doi: 10.1016/j.rmr.2018.10.010 [published Online First: 2018/11/16]

44. Answer given by Mr Andriukaitis on behalf of the Commission, Parliamentary questions, available at:
http://www.europarl.europa.eu/sides/getAllAnswers.do?reference=P-2016-009191&language=ES#def1 9 January 2017

45. Statement on the toxicological evaluation of novel heatnot-burn tobacco products, COMMITTEES ON TOXICITY, CARCINOGENICITY AND MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT, COC and COM), available at:
https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2017/statement-on-heat-not-burn-tobacco-products, 11 December 2017.

46. LaVito A. In high-stakes votes, FDA advisors say evidence doesn't back Philip Morris' claims.
https://www.cnbc.com/2018/01/25/philip-morris-stock-falls-as-committee-reviews-iqos-claims.html. *CNBC Health Care* 25.01.2018.

47. da Costa e Silva V. Opening of the Eighth session of the Conference of the Parties (COP8) , Keynote speech by Dr Vera Luiza da Costa e Silva, Head of the WHO FCTC Secretariat.
http://www.who.int/fctc/secretariat/head/statements/2018/opening-cop8/en/ , 1st October 2018 (accessed on 21.11.2018) [

48. WHO. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.
http://monographs.iarc.fr/ENG/Classification/ 2014 [

49. IARC. IARC strenghthens its findings on several carcinogenic personal habits and household exposure, World Health Organisation, International Agency for Research on Cancer, available at http://www.iarc.fr/en/media-centre/pr/2009/pdfs/pr196_E.pdf. 02 November 2009