



# Examining the evidence for the health impact of combustion-free products: progress and prospects for tobacco harm reversal and reduction

Riccardo Polosa<sup>1,2,3</sup>

Received: 20 August 2021 / Accepted: 25 August 2021 / Published online: 15 September 2021  
© The Author(s) 2021

**Keywords** Heated tobacco products · E-cigarette · Smoking cessation · Switching trials · Tobacco harm reduction · Biomarkers

Chronic inhalational exposure to the mixture of more than 8000 harmful and potentially harmful chemical constituents that transfer into cigarette smoke during tobacco combustion can cause progressive functional alterations and structural damage in the human body, which result in numerous medical conditions affecting primarily the respiratory and cardiovascular systems [1, 2].

The key to reducing the negative health effects of smoking is to avoid chronic exposure to chemicals released during the tobacco combustion of conventional cigarettes. This can be achieved either by smoking cessation programs, which include prescription medications (varenicline, bupropion, nicotine replacement therapy) and counselling [3] or by cigarette substitution with combustion-free products, which include e-cigarettes and heated tobacco products (HTPs) [4].

Almost certainly smoking cessation programs and switching trials with non-combustible sources of nicotine would produce significant health improvements, thus confirming what might reasonably be predicted from what is already common knowledge on chemical composition of combustible cigarettes smoke and pathogenesis of smoking-related diseases. Switching from cigarettes to combustion-free products has been shown to improve respiratory outcomes in

patients with COPD [5, 6] and to lower blood pressure in patients with hypertension [7]. Although these preliminary studies led to the expected results (i.e. that switching has similar clinical and functional benefits as quitting), their study design, sample size and reporting methods were not ideal.

To reassure health and regulatory authorities, larger prospective studies on the long-term health impact of combustion-free nicotine delivery products (C-F NDPs) are needed. It is essential to provide high quality clinical information on the harm reduction/reversal potential of CF-NDPs as a substitute for conventional cigarettes for long-term use; switching studies may form an integral part of regulatory submissions to the US Food and Drug Administration (FDA) when seeking authorization to market a novel product as a modified-risk tobacco product (MRTP) [8].

Gale et al. describe their approach to substantiating the potential for harm reduction/reversal of a newly marketed HTP in their carefully designed switching trial, published in *Internal and Emergency Medicine* [9].

The HTP device in their study (glo) electronically heats (instead of burning) small tobacco sticks at temperatures below 250 °C to generate nicotine-containing aerosols. Because these aerosols are produced at temperatures below combustion (which generally begins at temperature above 400 °C), they contain much less harmful and potentially harmful chemicals than tobacco smoke, and the overall level of chemical exposure in exclusive HTP users is considerably lower than in smokers [10]. Gale et al. executed the valuable scientific step of performing a reality check on the prediction that avoiding exposure to combustible cigarettes smoke by switching to much less harmful HTPs would almost certainly produce significant health improvements.

✉ Riccardo Polosa  
polosa@unict.it

<sup>1</sup> Institute of Internal Medicine, UOC Medicina Interna e Urgenza, AOU “Policlinico-V. Emanuele”, via S. Sofia, 78-Ed. 4, p. 2, stanza 78, 95100 Catania, Italy

<sup>2</sup> Department of Clinical and Experimental Medicine, University of Catania, Catania, Italy

<sup>3</sup> Center of Excellence for the Acceleration of Harm Reduction (CoEHAR), Università di Catania, Catania, Italy

To verify this prediction, authors enrolled 506 participants in a 12-month randomised controlled study; smokers who did not intend to quit were randomised to either continue smoking cigarettes or switched to using the HTP device under investigation, while smokers who indicated they wanted to quit smoking were enrolled in a standard cessation program. In addition, a group of never smokers was also included as a reference group.

Subjects were tested monthly for “biomarkers of exposure” (to selected cigarette smoke toxicants) and “biomarkers of potential harm” (relative to oxidative stress, cardiovascular and respiratory disease, and cancer) including urine 11-dehydrothromboxane B2 (11-dTx B2), urine 8-epi-Prostaglandin F2 $\alpha$  type III (8-Epi-PGF2 $\alpha$  type III), white blood cell (WBC) count, plasma soluble intercellular adhesion molecule-1 (sICAM-1), serum high-density lipoprotein (HDL), exhaled breath (FeNO), forced expiratory volume in 1 s (FEV<sub>1</sub>) and total 4-(methylnitrosamino)-1-[3-pyridyl]-1-butanol (NNAL).

This study also included testing a biomarker called Acrylonitrile Haemoglobin Adduct N [2-cyanoethyl]valine (CEVal). CEVal is an important compliance check, which identifies if participants in the switching and cessation arm of the study had recently smoked cigarettes [11]. Compliance to exclusive HTPs use and complete adherence to smoking cessation protocols is paramount in a study substantiating harm reduction when switching away from combustible cigarettes or when stopping smoking. Failure to completely replace or stop cigarettes would reduce or nullify the expected changes in biomarkers of exposure and potential harm. Specific CEVal threshold levels allowed authors to define the complete switchers and abstainers in which to assess biomarker changes.

Using data collected from 332 subjects between baseline and day 180, it was found that switching to HTPs not only reduced exposure to cigarette smoke toxicants, but also improved several BoPH when compared to continuing to smoke. In particular, the reported changes in 11-dTx B2, 8-Epi-PGF2 $\alpha$  type III, WBC count, FeNO, and total NNAL (a potent pulmonary carcinogen in rodents) were directionally consistent with lessened health impact. In spite of the complete switch, the reported changes in BoPH, although statistically significant, were small, well within the variability of the tests, and as such of questionable clinical relevance. No significant changes were reported for sICAM-1, HDL, and FEV1. The inclusion of a smoking cessation arm is critical to provide context to changes observed when participants switch from smoking to the HTPs use; similar small (and lack of) changes in BoPH were also observed in those undergoing smoking cessation over the same period of time. Moreover, another large switching trial of 984 smokers allocated to continue smoking cigarettes or to use an HTP device (IQOS) for 6 months showed modest (but yet

clinically irrelevant) changes in HDL-C, WBC, FEV1, and total NNAL [12].

It is not surprising that there was no clinical impact. When quitting smoking, BoPH may improve, but the change may be gradual and may take years to become clinically relevant. Also, improvements in BoPH are most likely to occur in smokers who have already been affected by pathophysiological changes and structural damage. For example, no significant changes in pulmonary function tests have been ever reported in smokers with normal spirometry at baseline who quit after switching to e-cigarettes, compared to those continuing to smoke [13, 14]. Not to forget, the relatively short 6-month follow up of the study by Gale et al. is insufficient to show meaningful smoking cessation responsive BoPH improvements and a much longer period of observation is necessary. Final results will not be available until the end of 2021, when the 12-month results will be released. Once we can determine whether the reduction in BoPH is maintained throughout the study, we will also be able to fully appreciate the magnitude of harm reduction potential that may be achievable by switching exclusively to HTPs.

Lack of sensitive and clinically significant endpoints for efficient substantiation of smoking cessation and tobacco harm reduction/reversal has been long acknowledged [15]. Reframing health effect indicators that are specifically relevant to smoking cessation and switching trials is the logical next step; several promising candidate outcome measures should be considered. For the FDA, it is useful to explore the health effects of novel tobacco and nicotine products to better understand their impact, in addition to examining additional study endpoints for the evaluation of the short- and long-term effects in clinical studies [16].

At the University of Catania’s Center of Excellence for the Acceleration of Harm Reduction (CoEHAR), researchers are carefully examining a number of relatively unexplored indicators of health effects for the best possible detection of biological/physiological changes associated with stopping smoking and for use in regulatory science. These included imaging studies (e.g. high-resolution computed tomography, hyperpolarized magnetic resonance imaging, optical coherence tomography angiography, quantitative light-induced fluorescence scanning), digitized patient-reported outcomes (e.g. App-based questionnaires) as well as functional tests (e.g. impulse oscillometry, forced expiratory flow from 25 to 75% of vital capacity, maximal oxygen consumption, augmentation index, pulse wave velocity, mucociliary clearance transit time).

Results so far are promising and generally supportive of their value. For example, by measurement of mucociliary clearance transit time (MCCTT) researchers can detect early respiratory health changes in smoking cessation studies and switching trials. Chronic exposure to cigarette smoke is known to cause progressive structural damage and functional

alterations of the lungs, with loss of cilia, reduced ciliary beating, and airway epithelial mucus cell hyperplasia with mucus hypersecretion [17, 18]. Functional impairment and structural damage of the respiratory tract contribute to prolonged mucociliary clearance transit time (MCCTT) in smokers [19, 20] and stopping smoking may quickly reduce structural damage and restore cilia-mucus interaction [21, 22]. In a recent study we have shown that smokers who stopped smoking by switching to exclusive use of combustion-free nicotine delivery systems (such as ECs and HTPs) exhibited similar MCCTT as never and former smokers (23). It appears that MCCTT restoration occurs relatively soon after quitting. As well as being relevant to the investigation of possible health issues, the study's conclusions could be very valuable in assisting with the substantiation of harm reduction and reversal of adverse effects of combustion-free nicotine/tobacco products.

Considering that many smokers continue to smoke despite the health risks, combustion-free nicotine delivery technology has enormous potential to help reduce smoking rates. Researchers should keep committing to high quality research with the goal of accurately delineating the harm reduction potential of these new technologies and advancing the current understanding of their impact on human health.

**Funding** Open access funding provided by Università degli Studi di Catania within the CRUI-CARE Agreement.

### Compliance with ethical standards

**Conflict of Interest** RP is full tenured professor of Internal Medicine at the University of Catania (Italy) and Medical Director of the Institute for Internal Medicine and Clinical Immunology at the same University. In relation to his recent work in the area of respiratory diseases, clinical immunology, and tobacco control, RP has received lecture fees and research funding from Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, MSD, Boehringer Ingelheim, Novartis, Duska Therapeutics, and Forest Laboratories. Lecture fees from a number of European EC industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy nonprofit organizations. RP has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology & Immunology Specialists Network (IRIS) initiative. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, CV Therapeutics, Boehringer Ingelheim, Novartis, Duska Therapeutics, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl., Health Diplomats, and Sermo Inc. RP has served on the Medical and Scientific Advisory Board of Cordex Pharma, Inc., CV Therapeutics, Duska Therapeutics Inc, Pfizer, and PharmaCielo. RP is also founder of the Center for Tobacco prevention and treatment (CPCT) at the University of Catania and of the Center of Excellence for the acceleration of HArm Reduction (CoEHAR) at the same University, which has received support from Foundation for a Smoke Free World to conduct 8 independent investigator-initiated research projects on harm reduction. RP currently involved in a patent application con-

cerning an app tracker for smoking behaviour developed for ECLAT Srl. RP is also currently involved in the following pro bono activities: scientific advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League), the Consumer Advocates for Smoke-free Alternatives (CASAA) and the International Network of Nicotine Consumers Organizations (INNCO); Chair of the European Technical Committee for standardization on “Requirements and test methods for emissions of electronic cigarettes” (CEN/TC 437; WG4).

**Human and animal rights statement** This commentary does not contain any studies directly involving participants or animals.

**Informed consent** Formal consent is not required for a commentary

**Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

### References

1. U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress: a report of the surgeon general. Atlanta: US 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. <https://www.ncbi.nlm.nih.gov/books/NBK179276/>
2. U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the surgeon general. Atlanta: 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. 2010 <https://www.ncbi.nlm.nih.gov/books/NBK53017/>
3. U.S. Department of Health and Human Services. Smoking Cessation: A Report of the Surgeon General [Internet]. Washington (DC): U.S. Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. <https://www.ncbi.nlm.nih.gov/books/NBK555591/>
4. O'Leary R, Polosa R (2020) Tobacco harm reduction in the 21st century. *Drugs Alcohol Today* 20(3):219–234. <https://doi.org/10.1108/DAT-02-2020-0007>
5. Polosa R, Morjaria JB, Prosperini U, Busà B, Pennisi A, Gussoni G, Rust S, Maglia M, Caponnetto P (2021) Health outcomes in COPD smokers using heated tobacco products: a 3-year follow-up. *Intern Emerg Med* 16(3):687–696. <https://doi.org/10.1007/s11739-021-02674-3>
6. Polosa R, Morjaria JB, Prosperini U, Busà B, Pennisi A, Malerba M, Maglia M, Caponnetto P (2020) COPD smokers who switched to e-cigarettes: health outcomes at 5-year follow up. *Ther Adv Chronic Dis* 10(11):2040622320961617. <https://doi.org/10.1177/2040622320961617>

7. Polosa R, Morjaria JB, Caponnetto P, Battaglia E, Russo C, Ciampi C, Adams G, Bruno CM (2016) Blood pressure control in smokers with arterial hypertension who switched to electronic cigarettes. *Int J Environ Res Public Health* 13(11):1123. <https://doi.org/10.3390/ijerph13111123>
8. Food and Drug Administration (2012) Modified risk tobacco product applications. Draft guidance for industry. Docket No. FDA-2012-D-0071. *Fed Reg* 77:20026–20030
9. Gale N, McEwan M, Camacho OM, Hardie G, Proctor CJ, Murphy J (2021) Changes in biomarkers after 180 days of tobacco heating product use: a randomised trial. *Intern Emerg Med*. <https://doi.org/10.1007/s11739-021-02798-6> (**Epub ahead of print**)
10. Gale N, McEwan M, Camacho OM, Hardie G, Murphy J, Proctor CJ (2021) Changes in biomarkers of exposure on switching from a conventional cigarette to the glo tobacco heating product: a randomized Controlled Ambulatory Study. *Nicotine Tob Res* 23(3):584–591. <https://doi.org/10.1093/ntr/ntaa135>
11. Camacho OM, McEwan M, Gale N, Pluym N, Scherer M, Hardie G, Murphy J (2021) Use of the acrylonitrile haemoglobin adduct N-(2-cyanoethyl)valine as a biomarker of compliance in smokers switching to tobacco heating products. Preprints. <https://doi.org/10.20944/preprints202108.0085.v1>
12. Lüdicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Peitsch M, Weitkunat R (2019) Effects of switching to a heat-not-burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: a randomized trial. *Cancer Epidemiol Biomark Prev* 28(11):1934–1943. <https://doi.org/10.1158/1055-9965>
13. Cibella F, Campagna D, Caponnetto P et al (2016) Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)* 130(21):1929–1937
14. Cravo AS, Bush J, Sharma G et al (2016) A randomised, parallel group study to evaluate the safety profile of an electronic vapour product over 12 weeks. *Regul Toxicol Pharmacol* 81(Suppl 1):S1–S14
15. Polosa R (2015) Electronic cigarette use and harm reversal: emerging evidence in the lung. *BMC Med* 18(13):54. <https://doi.org/10.1186/s12916-015-0298-3>
16. FDA, HHS & CTP. Premarket tobacco product applications for electronic nicotine delivery systems guidance for industry (2019). <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-tobacco-product-applications-electronic-nicotine-delivery-systems-ends>
17. Cohen D, Arai SF, Brain JD (1979) Smoking impairs long-term dust clearance from the lung. *Science* 204:514–517
18. Domagala-Kulawik J (2008) Effects of cigarette smoke on the lung and systemic immunity. *J Physiol Pharmacol* 59(Suppl 6):19–34
19. Pagliuca G, Rosato C, Martellucci S, de Vincentiis M, Greco A, Fusconi M et al (2015) Cytologic and functional alterations of nasal mucosa in smokers: temporary or permanent damage? *Otolaryngol Head Neck Surg* 152(4):740–745
20. Emma R, Caponnetto P, Cibella F, Caruso M, Conte G, Benfatto F, Ferlito S, Gulino A, Polosa R (2020) Short and long term repeatability of saccharin transit time in current, former, and never smokers. *Front Physiol* 18(11):1109. <https://doi.org/10.3389/fphys.2020.01109>
21. Ramos EM, De Toledo AC, Xavier RF et al (2011) Reversibility of impaired nasal mucociliary clearance in smokers following a smoking cessation programme. *Respirology* 16(5):849–855
22. Utiyama DM, Yoshida CT, Goto DM et al (2016) The effects of smoking and smoking cessation on nasal mucociliary clearance, mucus properties and inflammation. *Clinics (Sao Paulo)* 71(6):344–350
23. Polosa R, Emma R, Cibella F, Caruso M, Conte G, Benfatto F, Ferlito S, Gulino A, Malerba M, Caponnetto P (2021) Impact of exclusive e-cigarettes and heated tobacco products use on mucociliary clearance. *Ther Adv Chron Dis*. <https://doi.org/10.1177/20406223211035267> (**Published 2021 Aug 12**)

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.