Ther Adv Chronic Dis
2021, Vol. 12: 1–9
DOI: 10.1177/20406223211035267

Impact of exclusive e-cigarettes and heated tobacco products use on muco-ciliary clearance

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Abstract

Background: Tobacco smoking impairs mucociliary clearance (MCC) efficiency as shown by prolonged saccharin test transit time (STTT). Avoiding exposure to tobacco smoke from combustible cigarettes may restore MCC function and former smokers have been shown to exhibit similar STTT as never smokers. The impact on STTT of switching from smoking to combustion-free tobacco products such as e-cigarettes (ECs) and heated tobacco products (HTPs) is not known.

Methods: We report STTT of exclusive EC and HTP users. Test results were compared with those obtained in current, former, and never smokers.

Results: STTT were obtained from 39 current, 40 former, 40 never smokers, and from 20 EC and 20 HTP users. Comparison of STTT values showed significant difference among the five study groups ($p < 0.00001$) with current smokers having a median [interquartile range (IQR)] STTT of 13.15 min, which was significantly longer compared with that of all other study groups. In particular, compared with former (7.26 min) and never smokers (7.24 min), exclusive EC users and exclusive HTP users had similar STTT at 7.00 and 8.00 min, respectively.

Conclusion: Former smokers who have switched to exclusive regular use of combustion-free nicotine delivery systems (i.e., ECs and HTPs) exhibit similar saccharin transit time as never and former smokers. This suggests that combustion-free nicotine delivery technologies are unlikely to have detrimental effects on MCC function.

Keywords: e-cigarette, heated tobacco products, mucociliary clearance transit time, saccharin test, smoking

Received: 13 May 2021; revised manuscript accepted: 7 July 2021.

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Introduction

In addition to causing cardiovascular diseases, cancer, and chronic obstructive pulmonary diseases (COPD),[1,2] chronic exposure to a range of toxic chemicals in the cigarette smoke can cause progressive structural damage and functional alterations of the airways, with loss of cilia,[3,4] reduced ciliary beating,[5,6] and airway epithelial mucus cell hyperplasia causing mucus hypersecretion.[7,8] Tobacco combustion in conventional cigarettes is known to release a multitude of harmful and potentially harmful chemical constituents including phenol, formaldehyde, and acrolein,[9] which have been shown to be cilia-toxic.[10] Disruption of the mucociliary clearance (MCC) function may contribute to inflammation and obstruction of the small airways,[11] and increased susceptibility to respiratory infections.[12–14]

Abstaining from tobacco smoking may reduce structural damage and restore cilia-mucus interaction. Former smokers have been shown to exhibit similar MCC transit time (MCCTT) as never smokers,[15] and smoking cessation studies have demonstrated that MCC impairment can be reversed rapidly in quitters.[16,17] The demonstration that the cilia-mucus functional framework of smokers can be restored soon after stopping exposure to smoke toxicants suggests that measurement of MCCTT can be used as a sensitive biomarker of

physiological effect for the detection of early respiratory health changes in smoking cessation studies and switching trials of combustion-free nicotine delivery systems [e.g., e-cigarettes (EC), heated tobacco products (HTPs)].

Products that do not require combustion to deliver nicotine such as ECs and heated tobacco products (HTPs) are substituting conventional cigarettes globally.[18] Compared with conventional cigarettes, they offer substantial reduction in exposure to harmful and potentially harmful chemical constituents including phenol, formaldehyde, and acrolein[19–22] and, for this reason, combustion-free nicotine delivery systems are have been considered for smoking harm reduction.[23]

A significant reduction in combustion toxicants when stopping smoking can reverse the impairment of the cilia-mucus functional structure and exposure to aerosols generated from combustion-free nicotine delivery technologies is expected to be considerably less cilia-toxic. It is therefore hypothesized that substitution of cigarette smoking with the use of combustion-free nicotine delivery technologies may lead to faster MCCTT compared with current smokers.

To test this hypothesis, we carried out Saccharin tests – a non-invasive, well tolerated and simple to perform method that measures MCCTT – in a group of exclusive e-cigarettes and heated tobacco products users.[24] Test results were compared with data of current, former, and never smokers from our previous work with saccharin test.[25]

Methods

Study population

Smokers who attended a smoking cessation clinic (CPCT, Centro per la Prevenzione e Cura del Tabagismo of the University of Catania), or never smokers contacted among hospital staff, or through social media, were recruited. Study participants were defined as follows:

1. Current smokers: people smoking ⩾10 cigarettes per day, and with an exhaled carbon monoxide (eCO) level of ⩾7 ppm;
2. Former smokers: people not smoking for at least 3–6 months at the time of screening, and with an eCO level of <7 ppm;
3. Never smokers: people reporting having smoked less than 100 cigarettes in their lifetime,[26] and with an eCO level <7 ppm (to exclude subjects significantly exposed to environmental cigarette smoke);
4. EC users: people exclusively using vaping products daily and not smoking for at least 3–6 months after switching to their device, and with an eCO level of <7 ppm;
5. HTP users: people exclusively puffing HTPs daily and not smoking for at least 3–6 months after switching to their device, and with an eCO level of <7 ppm.

Study participants had to satisfy the following exclusion criteria:

- Any conditions that could impair cilia-mucus interaction or interfere with MCCTT measurements, such as:
  - Recent (less than 14 days) history of viral infection of the upper respiratory tract;
  - Conditions that may damage nasal mucosa (e.g., chronic rhinosinusitis, infectious rhinitis, allergic rhinitis, atrophic rhinitis, vasomotor rhinitis);
  - Respiratory conditions that may interfere with MCCTT measurements (e.g., COPD, asthma, bronchiectasis, cystic fibrosis);
  - Significant exposure to passive smoking (excludes current smokers);
  - Significant environmental/occupational exposure to pollution or chemicals (e.g., living in proximity of areas characterized by heavy vehicles traffic, or by presence of industrial fumes; employment in chemical/metallurgy industries);
  - Medications such as pain killers, sleeping pills, antihistamines.
- Poor individual ability to detect sweetness [i.e., being below the 25 mm mark on the 0–100 mm paper visual analog scale (VAS) for sweetness intensity rating];
- Current use of EC or HTPs (for current, former and never smokers only);
- Pregnancy.

The study was approved by the local Ethical Review Board (number 125/2019/empo, Comitato Etico Catania 1. AOU Policlinico Vittorio Emanuele) and participants gave written informed consent prior to participation in the study.

Study design

This cross-sectional study was designed to assess and compare MCCTT among five study populations: (1) current smokers; (2) former smokers; (3) never smokers; (4) exclusive EC users (former smokers); and (5) exclusive HTP users (former smokers). Study groups were matched for age and gender by using a dedicated macro in the SAS software. After a screening visit, subjects were invited to attend for a saccharin test.

At screening, eligibility criteria (socio-demographic data, medical history, medication usage, and tobacco products history) were verified. Potential participants were tested for exhaled CO and their ability to detect sweetness. Perception of sweetness intensity was rated by using a 0–100 mm paper VAS. After rinsing the mouth with tap water and wiping the tongue dry with a paper towel, subjects were instructed to smear a crushed saccharin tablet (Mini-sweeteners; Hermesetas; Switzerland) all around the surface of their tongue. The sodium saccharin content for Hermesetas mini tablets is 11.8 mg/tablet.

They then were asked to rate the intensity of sweetness perception on a 0–100 mm paper VAS. Sweetness intensity ratings ranged from "not at all sweet" (at 0 mm) to "extremely sweet" (at 100 mm). Anybody below the 25 mm mark on the VAS was excluded from participation. Eligible subjects were then invited to attend the saccharin test visit. They were asked to refrain from drinking coffee/caffeinated drinks for at least 4 h prior to the study visit. Smokers were asked not to smoke, EC users not to vape, and HTP users not to puff their device for at least 1 h prior to the saccharin test visit. At saccharin test visits, eligibility criteria were verified once again. Before commencing the saccharin test, subjects' nose was rinsed with warm saline (NaCl 0.9% solution). After asking participants to acclimate at controlled environmental conditions (temperature 21–24°C; relative humidity 30–50%) for at least 45 min, saccharin test transit times (STTT) were measured.

Saccharin test method

After nasal washing with warm saline, participants were invited to acclimate in an examination room optimized for ambient temperature and humidity (i.e., temperature 21–24°C; relative humidity 40–60%). After 45 min acclimation, participants were invited to slightly raise and tilt the head backwards. Whilst illuminating a nostril (indicated by the subject as the one allowing better nasal breathing – the same nostril will be used for all tests providing patency is maintained throughout study visits) with a medical headlight and widening it using a nasal speculum, the research investigator (or ENT research nurse) identified the small crest that marks the tip of the inferior turbinate. A nipper clasping a saccharin tablet was guided through the speculum and the tablet was gently placed horizontally on the medial face of the inferior turbinate, about 1 cm behind its anterior end. The nipper and nasal speculum were withdrawn, paying attention not to trigger any sneezing. Subjects were then invited to return their heads to a straight position and a chronometer was started. Subjects were asked to swallow some saliva a couple of times every minute until perceiving the "sweet taste" of saccharin. Subjects were instructed to avoid to sniff, sneeze, eat, drink, walk, talk, cough, scratch, or blow their nose. The STTT has been shown to have significant short- and long-term reproducibility.[25,27–29]

Statistical analysis

Based on data from previous saccharin test studies comparing current, former, and never smokers, we estimated that a sample of at least 20 subjects for each group was adequate to obtain a power greater than 90% with a type I error (alpha) smaller than 0.05 (5%) in an equivalence comparison. The upper limit of normality (ULN) was calculated by computing the value corresponding to the mean + standard deviation (SD) $\times$ 1.64 from the distribution curve of the results of the MCCTT measurements in never smokers. Kolmogorov–Smirnov test was performed to assess the data distribution. Categorical data were summarized by counts and percentages; continuously distributed data, with symmetrical distribution, were summarized using the mean [standard error (SE)]; continuously distributed data, with skewed distribution, were summarized using the median [interquartile range (IQR)]. Study groups comparisons were carried out by Chi-square test, ANOVA, and Kruskal–Wallis test for categorical, continuously symmetric, and continuously skewed datasets, respectively. Moreover, cross-comparison between groups were calculated using pairwise Wilcoxon test with Holm

Table 1. Baseline characteristics of study subjects. Data are reported as mean ± SD, median (IQR), n/N unless otherwise stated.

	Never smokers	Current smokers	Former smokers	Exclusive HTP users	Exclusive EC users[a]	*p* value
Age	32.5 (25–41)	31 (24.5–44)	33 (25.75–41.25)	34.5 (26.5–44.75)	33.5 (25.75–42)	0.979
Female/Male	20/20	19/20	20/20	10/10	10/10	0.991
BMI	23.4 ± 3.2	24.9 ± 5.0	24.0 ± 4.4	25.2 ± 4.5	24.0 ± 4.8	0.092
Exhaled CO	3 (2–4)	19 (15–22.5)	2.5 (1.8–5.0)	3 (2–5)	3 (1.8–4.3)	<0.0001
Pack/years	NA	12.5 (6.2–20.4)	15 (5.1–25.4)	16.3 (9.2–26.6)	12 (7.0–28.0)	0.954
Cigarettes/day	NA	15 (11–20)	20 (15–25)*	20 (12–25)*	16 (11–20)	0.268
Smoking duration in years	NA	14.5 (7.25–21)*	15.5 (8.75–23)*	15 (9.25–20)*	14 (7.75–24)*	0.810
FTND	NA	6 (5–7)	NA	NA	NA	–
E-liquid/day (ml) Consumption	NA	NA	NA	NA	2.7 ± 1.0	–
E-liquid nicotine strength (mg/ml)	NA	NA	NA	NA	13.6 ± 2.7	–
Vaping duration in months	NA	NA	NA	NA	7.5 (6–8.0)	–
Tobacco sticks/day	NA	NA	NA	14 ± 2.05	NA	–
HTP use duration in months	NA	NA	NA	7 (6–7.5)	NA	–

[a]All e-cigarette users had devices with refillable tanks/pods.
*Refers to previous smoking (prior to quitting).
BMI, body mass index; CO, carbon monoxide; EC, e-cigarette; FTND, Fagerstrom test for nicotine dependence; HTP, heated tobacco product; IQR, interquartile range; NA, not available; SD, standard deviation.

correction for multiple testing. All analyses were considered significant with a p value < 0.05. R version 3.4.3 was utilized for data analysis and generation of graphs.

Results

Study participants

Complete analysis on the saccharin test was carried out in 159 subjects: 79F/80M with a median (IQR) age of 32 (25–42) years (Table 1). No significant differences were observed among the study groups, with the exception of exhaled eCO levels, which were significantly ($p < 0.0001$) elevated in current smokers compared with never smokers, former smokers, exclusive HTP users, and exclusive EC users.

MCCTT comparison between study groups

Comparison of MCCTT values showed significant difference among the five study groups ($p < 0.00001$); current smokers had a median (IQR) MCCTT of 13.15 (9.89–16.08) min, which was significantly longer compared with that of never smokers at 7.24 (5.73–8.73) min, former smokers at 7.26 (6.18–9.17) min, exclusive EC users at 7.00 (6.38–9.00) min, and exclusive HTP users at 8.00 (6.00–8.00) min (Figure 1).

Pairwise comparisons between each study group showed that significant differences occurred only when current smokers were compared with any other study group, whereas no significant differences were observed for any other between-group comparisons (Table 2).

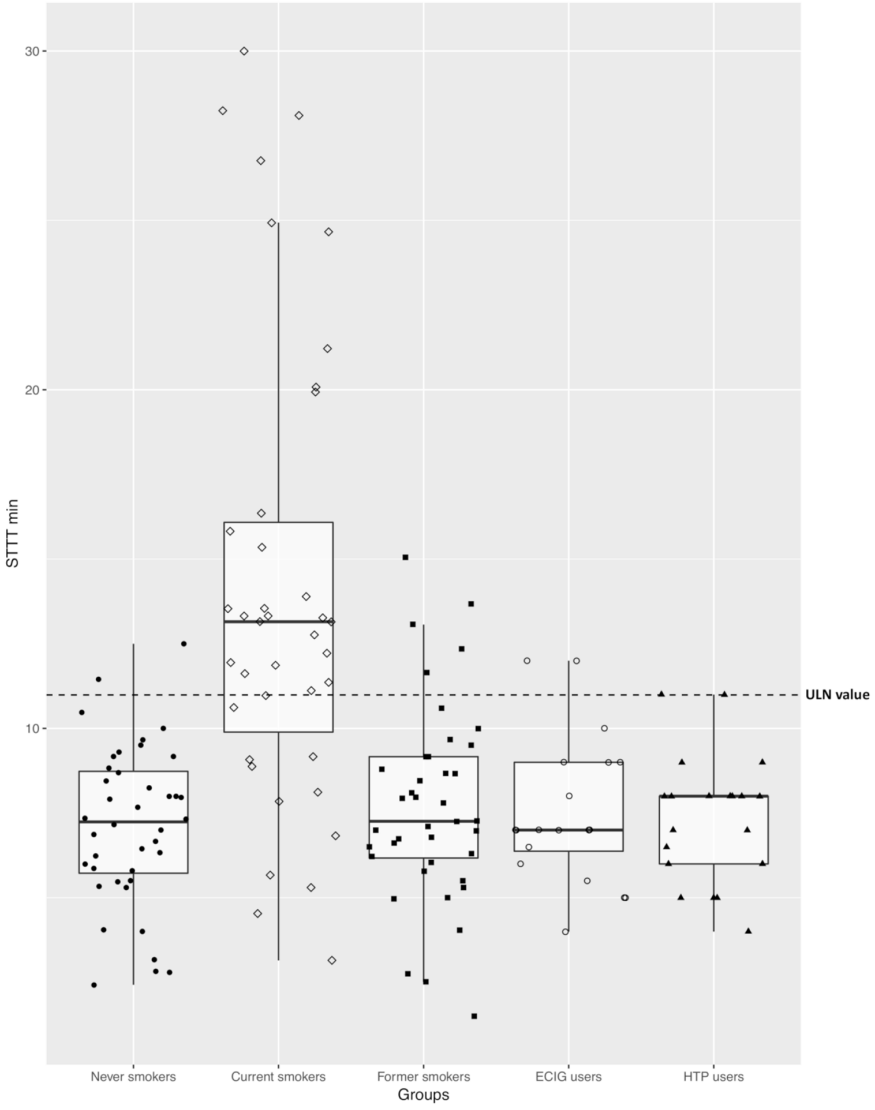

Figure 1. STTT measurements among never smokers (closed circles), current smokers (open diamonds), former smokers (closed squares), exclusive EC users (open circles), and exclusive HTP users (closed triangles). The median STTT (IQR) was prolonged only in current smokers, compared with other study groups. The calculated ULN was 10.99 min. The overall *p* value was calculated by Kruskal–Wallis test.
EC, e-cigarette; HTP, heated tobacco product; IQR, interquartile range; STTT, saccharin test transit time; ULN, upper limit of normality.

The calculated ULN of 10.99 min in never smokers was used as a cut-off point for abnormal MCCTT measurements. As expected, most of current smokers (27/39; 69.2%) had an MCCTT value above the ULN, whereas only 12.5% (5/40) former smokers, 10% (2/20) exclusive EC users, and 10% (2/20) exclusive HTP users had MCCTT values above the ULN.

Discussion

This is the first study to investigate saccharin transit time in EC and HTP users. Compared with never and former smokers, saccharin transit time in current cigarette smokers was nearly twice as long (7.24 and 7.26 min *versus* 13.15 min) and remarkably similar transit times were also observed in ECs (7.00 min) and HTPs users (8.00 min). Moreover, 90% of transit time measurements taken from EC users or HTP users were well within the upper limit of normal.

With a saccharin transit time that is similar to that of former and never smokers, EC and HTP users exhibit no significant impairment of MCC. Considering that exclusive EC and HTP users in

Table 2. Pairwise comparisons between study groups.

Pairwise adjusted *p* values[a]	EC users	HTP users	Never smokers	Former smokers	Current smokers
EC users	–	1	1	1	0.00016
HTP users	1	–	1	1	<0.0001
Never smokers	1	1	–	1	<0.00001
Former smokers	1	1	1	–	<0.00001
Current smokers	0.00016	<0.0001	<0.00001	<0.00001	–

[a]Adjusted *p* values were calculated using Kruskal–Wallis test with Holm correction for multiple testing. *p* values < 0.05 were considered significant. *p* value $= 1$ indicates no difference between each pairwise comparison.
EC, e-cigarette; HTP, heated tobacco product.

our study have been abstaining from smoking only recently (3–36 months), MCC restoration after smoking cessation appears to occur within a relatively short time period after quitting. Prospective studies are required to clarify the time-course of MCCTT restoration after smoking cessation.

In agreement with the findings of this paper, cigarette smoking slows down MCCm and abstaining from smoking quickly restores MCC efficiency.[16,17] However, that regular users of ECs and HTPs exhibited no lengthening of STTT indicates that combustion-free nicotine delivery technologies are unlikely to have detrimental effects on MCC function. This is a novel finding and requires explanation.

Whereas chronic exposure to toxic chemicals generated during tobacco combustion is known to cause functional alterations and structural damage of ciliated airway epithelial cells,[3–6] very little is known about the effect of aerosol emissions from combustion-free nicotine delivery technologies. By completely substituting ECs for combustible tobacco cigarettes, users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes is greatly reduced.[19–21] Same marked reductions in toxicants exposures have been reported for HTPs compared with cigarettes.[22,30,31]

Primary human bronchial epithelial cells exposed to cigarette smoke showed a clear reduction in mucus-secreting cells and their secretion activity as well as in cilia beating, with much less pronounced effects for the cells treated with EC aerosol.[32] In an experimental model of excised bullfrogs' palates, although exposure to EC aerosol emission had a modest inhibitory effect on mucus transport velocity, tobacco smoke exposure of the palates had a remarkable inhibitory effect.[33] In a whole-body intense exposure protocol, no significant slowing in MCC by radioisotope technique was observed in mice exposed for 1 week to high levels of EC emission aerosols, and trachea histology of sacrificed animals showed no apparent damage of the ciliated epithelial cells.[34] Under normal condition of use, the level of cilia-toxic chemicals (including phenol, formaldehyde, and acrolein) in EC and HTP aerosol emissions are 80–99% lower compared with cigarette smoke.[19–22] Accordingly, exposure to aerosols generated from combustion-free nicotine delivery technologies is expected to be considerably less cilia-toxic. These observations may suggest that combustion-free nicotine delivery technologies are unlikely to have adverse effects on MCC function, and add to the evidence that these products do not appear to pose a significant respiratory health hazard.[35]

Please note this study is about relative (not absolute) MCCTT changes from smoking when completely substituting conventional cigarettes for non-combustible sources of nicotine. Findings were not unexpected. The conclusion is consistent with what we have learned about tobacco smoke chemical composition and cilia dysfunction/destruction over the last 40–50 years, that we are almost certain that stopping smoking (including by substituting tobacco cigarettes with non-combustible sources of nicotine) would produce substantial improvement in MCCTT.

Some of the strengths of this study included: (1) exclusion of participants with any condition that

could interfere with the results of saccharin test; (2) careful characterization of participants *via* detailed smoking, vaping, and HTP use history; (3) biochemical verification of participants' smoking status by exhaled CO; (4) meticulous preparation and competent conduct of our standardized saccharin test; and (5) being one of the largest MCCTT study ever conducted.

When interpreting the study findings, many factors need to be considered. First, the reported lack of difference when comparing small study groups (i.e., EC and HTP) should be interpreted with caution. Yet, power analysis of the collected data indicates that a sample of at least 20 subjects for each group is adequately powered to detect significant differences in MCCTT. Moreover, careful examination of the individual saccharin test data on a case-by-case basis revealed identical 90% distribution of the measurements within the ULN value for both EC and HTP. Remarkably, significant differences were always reported when current smokers were included in all pairwise comparisons, confirming the superior discriminatory capability of the saccharin test. Second, EC and HTP users in this study had relatively short duration of exposure (vaping and HTP usage history ranging from 3 to 36 months) that may have not been sufficient to show an effect. In addition, no EC user consumed more than 5 ml e-liquid/day and no HTP users puffed more than 15 sticks/day. Duration (years) and intensity of smoking (cigarettes/day) are significant predictors of MCCTT impairment among smokers, with high intensity smoking (average of 39 cigarettes/day) nearly doubling MCCTT, low smoking intensity (average of 9 cigarettes/day) not having much of an effect[36] and smoking duration >5 years showing twice the STT compared with smokers with a much shorter smoking history and to non-smokers.[37] It is possible that the reported lack of impact on STT among EC and HTP user could have been due to low-intensity aerosol exposure, but switching from combustion *versus* no-combustion consistently restores MCC to near-normal STTT values. Third, study samples consisted of relatively young subjects and their response to the saccharin test may not be representative of the general population; additional studies with more representative age groups are needed. Fourth, with the exception of a single GLO user, all other participants in the HTP study group were using IQOS; HTP results are essentially product specific. Conversely, EC users were consuming different types of vaping products. Last but not least, it is acknowledged that cross-sectional studies have limitations when trying to establish a causal relationship. Nonetheless, we provided enough information on temporal relations and "dose" of smoking exposure (i.e., absence of smoking exposure) for the populations under investigation to infer causality. Moreover, near-normal STTT values were consistently found in all study groups not exposed to combustion toxicants.

In relation to the wider implications of this study, it is our opinion that measurement of saccharin transit time can be used as a sensitive biomarker of physiological effect for the detection of early respiratory health changes in smoking cessation studies and switching trials. In addition, the saccharin test may represent a unique valuable endpoint for medical and regulatory research applied to combustion-free tobacco products (e.g., e-cigarettes, heated tobacco products, oral tobacco/nicotine products, etc.), smoking cessation medications, and pharmacological interventions for lung diseases characterized by defective mucus clearance.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This research was supported by University grant no. 2040101-UPB20722142112 of "Ricerca Scientifica Finanziata dall'Ateneo di Catania".

Conflict of interest statement

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 no-profit organizations. RP has also received grants from European Commission initiatives (U-BIOPRED and AIRPROM) and from the Integral Rheumatology and 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., and Health Diplomats. 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 eight independent investigator-initiated research projects on harm reduction. 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). MM is a full-time employee of the University of Piemonte Orientale. MM has received lecture fees and research funding from GSK Italy, Astra-Zeneca, Chiesi, Boehringer, Grifols, Menarini, Guidotti and Vitalair. MM has also served as a consultant for ALK, Astra-Zeneca. SF and FC are full-time employee of the University of Catania and National Research Council of Italy, respectively and have no relevant conflict of interest to declare. AG, PC, GC, MC, FB and RE are fixed-term researchers at University of Catania and have no relevant conflict of interest to declare.

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