

## LETTER TO THE EDITOR | *Electronic Cigarettes: Not All Good News?*

### Letter to the Editor: Pulmonary toxicity of electronic cigarettes: more doubts than certainties

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TO THE EDITOR: In a recent issue of the *American Journal of Physiology-Lung Cellular and Molecular Physiology*, we read with great interest the review article by Chun et al. (2) about potential pulmonary effects of electronic cigarettes (ECs). This is a timely topic, and the authors do a comprehensive job of highlighting the chemical components of ECs, their relevance to the lung in the context of potential toxicity, and the approaches and challenges to the study of ECs. However, the main problem we have with this review article is that the authors have systematically ignored contradictory evidence, failed to consider the impact of significant methodological limitations in most studies, and disregarded the uncertain relevance of in vitro and animal studies to humans. Thus, in the end, this article is raising more doubts than certainties.

The problem of reporting selectively is illustrated by the systematic emphasis on negative findings while dismissing positive results. For example, when they discuss in vitro models of cell toxicity induced by exposure to EC aerosols, the absence of cytotoxicity was reported in three of the eight papers describing the phenomenon, despite very high exposure levels. Additionally, the relevance of data obtained from direct e-liquid exposures, instead of aerosol exposures, can be questioned. Intuitively, aerosol exposure is more relevant to the real-life situation.

The review examined studies reporting adverse effects but failed to include a range of clinical studies with smokers who switched to ECs (1, 3–5). These studies have consistently shown that ECs are unlikely to raise significant health concerns for the human respiratory tract under normal condition of use and showed improvement in many cases (1, 3–5). A more comprehensive study selection would have provided a more accurate reflection of the available research.

With regard to the health effects of EC aerosol emissions, projecting results from cell lines or animal studies to humans are highly speculative. These studies are not replicating normal conditions of use and lack standardized protocols for EC aerosol generation, relevant comparators (e.g., tobacco smoke), and dosimetry. Animal studies and in vitro systems often include chronic, high-dose exposures and don't approximate the type of exposure from human vaping, thus leading to overestimation of toxicological effects. Moreover, in vitro and animal studies do not take into account the impact of prior smoking history. This is important because harm that has

accumulated throughout many years of smoking does not disappear at the point of switching to vaping or quitting completely and may well introduce bias and lead to erroneous interpretation of the data. That poor methodology and lack of standardization are serious problems with these studies is also shown by the conflicting results with cytotoxicity, inflammatory cytokines release, and mutagenicity being present in some but not in other studies. The authors exaggerate the acute changes detected with highly sensitive respiratory tests in short-term experimental studies and fail to mention that they simply reflect the physiological response of the respiratory tract against transient irritation from EC aerosol. Transient effects of vaping on health measurements of short-term experimental studies in humans are clinically irrelevant and without prognostic value.

By placing a greater emphasis on potential risks of EC use, the authors fail to acknowledge that these products may represent a major opportunity for individual as well as public health.

#### DISCLOSURES

R. Polosa is full-time employee of the University of Catania, Italy. In relation to his work in the area of tobacco control, RP has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop smoking medications. He has also received support from The Consumer Advocates for Smoke-free Alternatives (CASAA) for publication and open access costs of one paper. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, ECITA (Electronic Cigarette Industry Trade Association, in the UK), Arbi Group Srl (the Italian distributor for Categoria electronic cigarettes), and Health Diplomat (consulting company that delivers solutions to global health problems with special emphasis on harm minimization). Lectures fees from a number of European electronic cigarette industry and trade associations (including FIVAPE in France and FIESEL in Italy) were directly donated to vaper advocacy no-profit organizations. He 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) and for The Consumer Advocates for Smoke-free Alternatives (CASAA); Chair of the European Technical Committee for standardization on "Requirements and test methods for emissions of electronic cigarettes" (CEN/TC 437; WG4). M. Caruso has no conflict of interest to disclose. C. Mendelsohn has received payments from Pfizer Australia, GlaxoSmithKline and Johnson & Johnson Pacific for teaching, consulting and conference expenses.

#### AUTHOR CONTRIBUTIONS

M.C. and R.P. drafted manuscript; M.C., C.P.M., and R.P. edited and revised manuscript; M.C., C.P.M., and R.P. approved final version of manuscript.

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