Assessment of E-cigarette impact on smokers: The importance of experimental conditions relevant to human consumption

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We read with great interest the work of Lee et al. (1), in which the authors measured DNA damage induced by nitrosamines in vitro in different cell types and in vivo in various organs of E-cigarette smoke-exposed mice. The authors conclude that E-cigarette smoke might contribute to lung and bladder cancer in humans.

We do agree with the data interpretation of Lee et al. (1) based on their experimental evidence, but we do not share their conclusions about the possibility of translating these results into real-life settings. The present study does not replicate normal conditions of use and lacks standardized protocols for E-cigarette aerosol exposure and dosimetry. To this regard, animal studies and in vitro systems often include chronic, high-dose exposures and do not approximate the type of exposure from human vaping, thus leading to extreme overestimation of toxicological effects (2).

In fact, if we consider that the overall bodyweight of the mice is about 25 g, then the daily dose of aerosol exposure in mice would appear to be at least 3,000 times higher than that of an average vaper of 75 kg (i.e., 75,000 g). This would imply nothing but intoxication from the aerosol mass and its content. In this regard, Waldum et al. (3) showed no microscopic or macroscopic lung tumors, nor any increase in pulmonary neuroendocrine cells, following long-term inhalation of nicotine. To explain such evident discrepancy between the two studies, it is important to note that rodents were exposed to much different levels of nicotine. This is a very important issue when using an animal model in the attempt to resemble the conditions of a real-life setting. In particular, the study of Waldum et al. (3) exposed animals to nicotine (100 ng/mL), giving twice the plasma concentration found in heavy smokers. In contrast, in the present study Lee et al. (1) exposed mice to nicotine (10 mg/mL) without reporting its plasma concentration in animals.

In addition, in vitro experimental conditions may not resemble those of humans. In particular, cell irradiation with UV (i.e., 1,500 J/m^2) seems to be much higher compared with other reports (i.e., 0.6 J/m^2) (4). As far as concerns pharmacological treatment, Lee et al. (1) used very different nicotine concentrations (BEAS-2B: 0, 100, 300, 1,000 μM; UROtsa: 0, 50, 100, 200 μM), which appear to be very high compared with other experimental conditions (i.e., 0.5 μM) (5). Similarly, nicotine-derived nitrosamine ketone concentrations 0, 10, 300, and 1,000 μM were very high compared with other previous reports (0.1 μM) (6). Finally, the positive evidence from real-life surveys and clinical studies of patients with respiratory conditions supporting health benefits with E-cigarette use is in stark contrast with the concerns raised in animal models (7). By placing a greater emphasis on potential risks of E-cigarette use, Lee et al. (1) fail to acknowledge that they may represent a major opportunity for individual as well as public health.

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Conflict of interest statement: R.P. is a full-time employee of the University of Catania, Italy. In relation to his work in the area of tobacco control, R.P. has received lecture fees and research funding from Pfizer and GlaxoSmithKline, manufacturers of stop-smoking medications. He has also served as a consultant for Pfizer, Global Health Alliance for treatment of tobacco dependence, Electronic Cigarette Industry Trade Association, UK, and Health Diplomats. Lecture 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. Although no research was ever funded by the industry, support contributing to publication/open access costs of the following papers was received by the e-cig/e-liquid industry: Happy Liquid for https://www.ncbi.nlm.nih.gov/pubmed/28337155; Ritchy Europe for https://www.ncbi.nlm.nih.gov/pubmed/27845734; Cuts Ice e-Liquid Laboratories for https://www.ncbi.nlm.nih.gov/pubmed/28477286; and VDLV e-Liquids for https://www.ncbi.nlm.nih.gov/pubmed/28362360. R.P. is currently Scientific Advisor for LIAF, Lega Italiana Anti Fumo (Italian acronym for Italian Anti-Smoking League) and Head of the European Technical Committee for standardization on'Requirements and test methods for emissions of electronic cigarettes' (CEN/TC 437; WG4).

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