Lion Shahab, PhD[1*], Maciej L. Goniewicz, PhD[2], Benjamin C. Blount, PhD[3], Jamie Brown, PhD[4], Robert West, PhD[1]

[1] Department of Epidemiology and Public Health, University College London, London, UK

[2] Department of Health Behavior, Roswell Park Cancer Institute, Buffalo, New York, USA

[3] Tobacco and Volatiles Branch, Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia, USA

[4] Department of Clinical, Educational and Health Psychology, University College London, London, UK

Conflict of Interest: LS has received an honorarium for a talk, an unrestricted research grant and travel expenses to attend meetings and workshops from Pfizer, a pharmaceutical company that makes smoking cessation products, and has acted as paid reviewer for grant awarding bodies and as a paid consultant for health care companies. MLG reports research grants from and served as an advisory board member to pharmaceutical companies that manufacture smoking cessation medications. JB has received unrestricted research funding from Pfizer to study smoking cessation. RW has received travel funds and hospitality from, and undertaken research and consultancy for, pharmaceutical companies that manufacture or research products aimed at helping smokers to stop. BCB has no conflicts of interest to declare.

Response to Aubin et al

Aubin and colleagues argue that in our article we have produced misleading claims regarding estimated risk reduction from switching from conventional cigarettes to e-cigarettes because duration of exposure is more important than degree of exposure in raising cancer risk. We acknowledge that assessing whether e-cigarette use actually reduces harm among conventional cigarette smokers is challenging and that the adverse health effects of tobacco are related to duration of use, not just exposure. However, both are essential causal factors and to the extent that risk is broadly proportionate to *either*, a reduction in degree *or* duration of exposure will yield a proportionate reduction in risk. This is borne out by the evidence. Epidemiological studies directly support a link between the degree of exposure to nitrosamines, and other tobacco-specific toxicants assessed in our study, with subsequent cancer risk in conventional cigarette smokers (1) as well as lifelong never smokers (2). Based on this evidence, it's likely that significantly reduced exposure in e-cigarette compared with cigarette users results in reduced cancer risk.

Aubin et al further argue that nicotine can have adverse effects. While it is important to acknowledge that nicotine is not risk-free, particularly for vulnerable populations, including pregnant women and adolescents, post-marketing surveillance of licensed nicotine products and the epidemiological evidence from adult users of snus (a form of smokeless tobacco that is low in carcinogens but high in nicotine) in Sweden indicate that such effects are small relative to other constituents of tobacco smoke (3).

Crucially, in the context of harm reduction it is important to quantify and compare risks. E-cigarette use can be expected to carry some risk, so adult conventional cigarette smokers who switch completely to e-cigarettes instead of quitting smoking without the aid of such a device will be worse off than they would have been. However, smokers who switch to e-cigarette use who would otherwise have carried on smoking will benefit from a reduction in risk. Thus, a key determinant of whether e-cigarette use produces a public health gain is whether it causes more people to stop smoking than would otherwise have been the case, while not leading to initiation of either product among never users, particularly youth (4). The only population level estimate undertaken thus far has been in England, and it used time series analysis to estimate an additional 20,000 ex-smokers per year linked temporally with the increase in prevalence of e-cigarette use (5).

1. Yuan JM, Gao YT, Murphy SE, Carmella SG, Wang R, Zhong Y, et al. Urinary levels of cigarette smoke constituent metabolites are prospectively associated with lung cancer development in smokers. Cancer Res. 2011;71(21):6749-57.
2. Yuan JM, Butler LM, Gao YT, Murphy SE, Carmella SG, Wang R, et al. Urinary metabolites of a polycyclic aromatic hydrocarbon and volatile organic compounds in relation to lung cancer development in lifelong never smokers in the Shanghai Cohort Study. Carcinogenesis. 2014;35(2):339-45.
3. Shields PG**.** Long-term nicotine replacement therapy: cancer risk in context. Cancer Prev Res (Phila). 2011;4(11):1719-23.
4. Cherng ST, Tam J, Christine PJ, Meza R**.** Modeling the Effects of E-cigarettes on Smoking Behavior: Implications for Future Adult Smoking Prevalence. Epidemiology. 2016;27(6):819-26.
5. Beard E, West R, Michie S, Brown J**.** Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. BMJ. 2016;354:i4645.