

Invalidity of an Oft-Cited Estimate of the Relative Harms of Electronic Cigarettes

In July 2013, a group of 12 experts in decision science, medicine, pharmacology, psychology, public health policy, and toxicology rated the relative harm of 12 nicotine-containing products by using 14 criteria addressing harms to self and others.¹ The group concluded that combustible cigarettes were the most harmful and that electronic nicotine delivery systems (electronic cigarettes or e-cigarettes) were substantially less harmful than combustible cigarettes. These results have been characterized and repeated in the popular media as e-cigarettes are “95% less risky” or “95% less harmful” than combustible cigarettes. However, as the authors noted in a sweeping statement regarding the shortcomings of their own work, “A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria.”¹(p224)

Despite this lack of hard evidence, Public Health England and the Royal College of Physicians endorsed and publicized the “95% less harmful” assertion.^{2,3} Senior Public Health England staff emphasized the “evidence” underlying the 95% figure, despite the evidence being lacking. Much has been written about the dubious validity of the “95% less harmful” estimate in 2014 to 2016, especially about the

paucity of research on the health effects of e-cigarettes available in 2013. After six years of e-cigarette-focused research, which has yielded a growing body of hard evidence regarding harm (see Appendix A, available as a supplement to the online version of this article at <http://www.ajph.org>, for a nonexhaustive list), the time has come to re-examine that estimate.

TODAY'S ELECTRONIC CIGARETTES ARE DIFFERENT

There is ample evidence that the range of e-cigarette products available today is very different from that in July 2013. The differences are such that, even if the 2013 estimate was valid then, it can no longer apply today. For example, in addition to using different materials and more numerous heating coils, many e-cigarettes today can attain power output that exceeds that of most over-the-counter 2013 models by 10 to 20 times (i.e., up to and sometimes exceeding 200 watts). Greater power increases the potential harms of e-cigarette use because more aerosol is produced that exposes users to increased levels of nicotine and other toxicants. It also increases bystander exposure to any harmful aerosol constituents

because users exhale more aerosol. In addition, greater power increases the potential for malfunction (e.g., the device exploding), which could harm users and bystanders.

Also, e-cigarette liquids have changed considerably from 2013, with widespread availability of thousands of flavors that use chemicals “generally recognized as safe” to eat but with unknown pulmonary toxicity. Perhaps the most striking change has been the pervasive marketing of liquids with protonated nicotine.⁴ Protonated nicotine (“nicotine salt”) is made by adding an acid to free-base nicotine, thus introducing another potential toxicant that was rare in 2013. Relative to free-base nicotine, aerosolized protonated liquid is less aversive to inhale, allowing users to increase the nicotine concentration of the liquid and likely increase their own nicotine

dependence. Protonated nicotine e-cigarette liquids are available today in concentrations greater than 60 milligrams per milliliter, and these liquids have become very popular, sparking a “nicotine arms race.”⁴

ELECTRONIC CIGARETTES CAUSE HARM TO CELLS

There is ample evidence, unavailable in 2013, that e-cigarette aerosols contain toxicants and that these aerosols are harmful to living cells in vitro and in vivo. For example, thermal degradation of e-cigarette liquid constituents can produce volatile aldehydes, which, at concentrations generated by e-cigarettes, display a variety of cardiorespiratory toxic effects. E-cigarettes can produce carcinogenic furans in addition to other toxicants such as chloropropanols. Even at room temperature, e-cigarette liquids can be unstable, producing irritating acetal compounds carried over into the aerosol. Numerous studies demonstrate that cell function is compromised following exposure to e-cigarette

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aerosol. Similarly, animals that are exposed to e-cigarette aerosols show clear indication of adverse consequences, including in models related to cardiovascular disease.

ELECTRONIC CIGARETTES HARM USERS

Recent evidence reveals that e-cigarette users show evidence of harm. For example, in a sample of healthy young occasional cigarette smokers who used an e-cigarette with or without nicotine, airway epithelial injury was observed in both conditions, with the authors concluding, “Thus, [e-cigarette] aerosol constituents could injure the respiratory system or worsen preexisting lung disease through a variety of mechanisms.”^{5(pL716)} Consistent with this report, wheezing, a symptom of potential respiratory disease, has been associated with e-cigarette use. E-cigarette use increases heart rate, blood pressure, and platelet activation, and decreases flow-mediated dilation and heart rate variability, effects that are prognostic of long-term cardiovascular risk. Indeed, a preliminary report indicates that e-cigarette users may be at increased risk for myocardial infarction and coronary artery disease.⁶

ELECTRONIC CIGARETTES INCREASE SMOKING RISK

Since 2013, numerous surveys have demonstrated that e-cigarette use is increasing among individuals who previously were naïve to nicotine and that these individuals are at increased risk for initiation of combustible cigarette smoking. As the US National Academies of

Sciences, Engineering, and Medicine concluded, “There is substantial evidence that [e-cigarette] use increases risk of ever using combustible tobacco cigarettes among youth and young adults.”^{7(p532)} To the extent that initial e-cigarette use is a causal factor in subsequent combustible tobacco smoking for an individual who would have otherwise never initiated smoking, e-cigarette use could be considered to be as harmful as tobacco smoking for that individual.

ELECTRONIC CIGARETTE AEROSOL IS NOT HARMLESS

Differences in toxicant content between e-cigarette aerosol and cigarette smoke, by themselves, cannot convey lesser lethality because toxicity depends upon both the extent and mode of use. For example, propylene glycol (PG) is one of the primary constituents of e-cigarette aerosol and is generally recognized as safe when eaten but, when injected intravenously over a period of days, is toxic. E-cigarette aerosols containing propylene glycol and vegetable glycerin, another common constituent, cause inflammation in human lungs, suggesting differing safety profiles for inhaled versus ingested propylene glycol and vegetable glycerin. Furthermore, as the toxicants in e-cigarette aerosol sometimes differ from cigarette smoke, so might any resulting e-cigarette-caused disease states. There is little doubt that exclusive e-cigarette users are unlikely to die from lung cancer that is caused by carcinogenic tobacco-specific nitrosamines or polycyclic aromatic hydrocarbons, toxicants largely absent from e-cigarette aerosols. What diseases they may die

of—and if their deaths are hastened by their e-cigarette use—will be part of the much-needed evidence base upon which valid risk estimates can be built.

CONCLUSIONS

In sum, a 2013 evidence-lacking estimate of the harm of e-cigarettes relative to combustible cigarettes has been cited often. However, since 2013, e-cigarette devices and liquids have changed. Evidence of potential harm has accumulated. Therefore, the evidence-lacking estimate derived in 2013 cannot be valid today and should not be relied upon further. Future estimates of the harm of e-cigarettes should be based on the evidence that is now available and revised accordingly as more evidence accrues.

CALL TO ACTION

The “95% safer” estimate is a “factoid”: unreliable information repeated so often that it becomes accepted as fact. Public health practitioners, scientists, and physicians should expose the fragile status of the factoid emphatically by highlighting its unreliable provenance and its lack of validity today, noting the many changes in e-cigarette devices and liquids, the accumulation of evidence of potential harm, the increased prevalence of use, and the growing evidence that e-cigarette use is associated with subsequent cigarette smoking. **AJPH**

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CONFLICTS OF INTERESTS

T. Eissenberg and A. Shihadeh are paid consultants in litigation against the tobacco industry and are named on a patent for a device that measures the puffing behavior of electronic cigarette users. In addition, as of September 2019, T. Eissenberg is a consultant in litigation against the electronic cigarette industry. S. Jordt reports receiving personal fees from Hydra Biosciences LLC and Sanofi SA and non-financial support from GlaxoSmithKline Pharmaceuticals outside the submitted work.

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