

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

Reply to “Letter to the Editor: Pulmonary toxicity of electronic cigarettes: more doubts than certainties”

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REPLY: In their letter to the editor, in this issue of the *American Journal of Physiology-Lung Cellular and Molecular Physiology*, Caruso and colleagues (3) reprise longstanding arguments that the tobacco industry uses to cast doubt on evidence linking smoking with disease (7) to question our conclusion that e-cigarettes pose important potential pulmonary risks (4). They argue that we have systematically ignored evidence, failed to consider significant methodological limitations, and disregarded the uncertain relevance of in vitro and animal studies to humans. We reject this characterization.

They criticize us for excluding four studies (2, 5, 11, 12). Two of the four (11, 12) are purely observational, finding that smokers who began using e-cigarettes and then reduced their cigarette consumption had improvement in symptoms and spirometry relative to smokers who did not reduce their cigarette consumption. In one of these studies (12), patients were included only if they were regularly using e-cigarettes on at least 2 follow-up visits at 24 mo. This design is biased toward including subjects who found e-cigarettes to be helpful. The other two studies (2, 5) refer to a single experiment in which smokers were randomized to e-cigarettes with three different nicotine concentrations. While less cigarette smoking was associated with improved symptoms and spirometry, this study did not include a control group of people who did not use e-cigarettes. As a result, none of these four studies permits any conclusions about the pulmonary toxicity of e-cigarettes.

Reducing exposure to cigarette smoke is a desirable goal that yields innumerable health benefits. However, the effect of e-cigarette use on smoking cessation was not tested in these four studies (nor was it a major focus of our review), and the evidence shows that overall e-cigarette use is associated with less smoking cessation, not more (9). More important, the implicit assumption that Caruso et al. (3) make is that e-cigarette aerosol is harmless, which as our review shows is not correct. Focusing exclusively on the effect of e-cigarettes on cessation among current smokers also ignores consistent evidence that e-cigarettes increase smoking initiation among non-smokers (1, 6, 14). As we (4) and others (8) have suggested, the overall health impact of e-cigarettes will depend both on their inherent toxicity and how they reduce or increase the consumption of traditional tobacco products.

All experimental models have limitations, but experimental models are well-established ways to generate important in-

sights into human toxicity. For example, by the early 1950s, the incidence of lung cancer was dramatically increasing and epidemiological data suggested cigarette smoking was the cause (15). Early attempts to induce tumors in animals with tobacco smoke frequently failed (10). However, a seminal 1953 study (16) exposed mice to skin “painting” with tobacco smoke tar three times a week for over a year and found that epithelial tumors frequently developed with a mean appearance time of 71 weeks. Mice were subsequently used to explore mechanisms of carcinogenesis with similarly intense exposure paradigms (13). The tobacco companies aggressively criticized these and other toxicological approaches on the grounds that they did not “replicate normal conditions of use” for decades despite the companies’ internal acceptance of these studies (7).

As detailed in our review (4), e-cigarettes have a different spectrum of toxicity than cigarettes. The case of diacetyl, the butter flavored food additive that has been proven to be an etiologic agent of obliterative bronchiolitis when inhaled, raises the possibility that various components of e-cigarettes may have unpredictable yet severe toxicity. Only industry will benefit if we await decades of human use to identify such toxicities, as we did with cigarettes. We argue that research should proceed at the cell culture, animal, and human levels simultaneously, leveraging the strengths of each approach while acknowledging their limitations.

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AUTHOR CONTRIBUTIONS

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REFERENCES

1. Best C, Haseen F, Currie D, Ozakinci G, MacKintosh AM, Stead M, Eadie D, MacGregor A, Pearce J, Amos A, Frank J, Haw S. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob Control*

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- tobaccocontrol-2017-053691, 2017. doi:[10.1136/tobaccocontrol-2017-053691](https://doi.org/10.1136/tobaccocontrol-2017-053691).
2. **Campagna D, Cibella F, Caponnetto P, Amaradio MD, Caruso M, Morjaria JB, Malerba M, Polosa R.** Changes in breathomics from a 1-year randomized smoking cessation trial of electronic cigarettes. *Eur J Clin Invest* 46: 698–706, 2016. doi:[10.1111/eci.12651](https://doi.org/10.1111/eci.12651).
 3. **Caruso M, Mendelsohn CP, Polosa R.** Letter to the Editor: Pulmonary toxicity of electronic cigarettes: more doubts than certainties. *Am J Physiol Lung Cell Mol Physiol* 313: 2017. doi:[10.1152/ajplung.00402.2017](https://doi.org/10.1152/ajplung.00402.2017).
 4. **Chun LF, Moazed F, Calfee CS, Matthay MA, Gotts JE.** Pulmonary toxicity of e-cigarettes. *Am J Physiol Lung Cell Mol Physiol* 313: L193–L206, 2017. doi:[10.1152/ajplung.00071.2017](https://doi.org/10.1152/ajplung.00071.2017).
 5. **Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, Cockcroft DW, Polosa R.** Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)* 130: 1929–1937, 2016. doi:[10.1042/CS20160268](https://doi.org/10.1042/CS20160268).
 6. **Conner M, Grogan S, Simms-Ellis R, Flett K, Sykes-Muskett B, Cowap L, Lawton R, Armitage CJ, Meads D, Torgerson C, West R, Siddiqi K.** Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. *Tob Control* tobaccocontrol-2016-053539, 2017. doi:[10.1136/tobaccocontrol-2016-053539](https://doi.org/10.1136/tobaccocontrol-2016-053539).
 7. **Glantz SA, ed.** *The cigarette papers*. Berkeley: University of California Press, 1996.
 8. **Kalkhoran S, Glantz SA.** Modeling the Health Effects of Expanding e-Cigarette Sales in the United States and United Kingdom: A Monte Carlo Analysis. *JAMA Intern Med* 175: 1671–1680, 2015. doi:[10.1001/jamainternmed.2015.4209](https://doi.org/10.1001/jamainternmed.2015.4209).
 9. **Kalkhoran S, Glantz SA.** E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med* 4: 116–128, 2016. doi:[10.1016/S2213-2600\(15\)00521-4](https://doi.org/10.1016/S2213-2600(15)00521-4).
 10. **Lorenz E, Stewart HL, Daniel JH, Nelson CL.** The effects of breathing tobacco smoke on strain A mice. *Cancer Res* 3: 123, 1943.
 11. **Polosa R, Morjaria JB, Caponnetto P, Caruso M, Campagna D, Amaradio MD, Ciampi G, Russo C, Fisichella A.** Persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who have switched to electronic cigarettes. *Discov Med* 21: 99–108, 2016.
 12. **Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, Bruno CM.** Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir Res* 17: 166, 2016. doi:[10.1186/s12931-016-0481-x](https://doi.org/10.1186/s12931-016-0481-x).
 13. **Proctor RN.** The history of the discovery of the cigarette-lung cancer link: evidentiary traditions, corporate denial, global toll. *Tob Control* 21: 87–91, 2012. doi:[10.1136/tobaccocontrol-2011-050338](https://doi.org/10.1136/tobaccocontrol-2011-050338).
 14. **Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD.** Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr* 171: 788–797, 2017. doi:[10.1001/jamapediatrics.2017.1488](https://doi.org/10.1001/jamapediatrics.2017.1488).
 15. **Wynder EL, Graham EA.** Tobacco smoking as a possible etiologic factor in bronchiogenic carcinoma; a study of 684 proved cases. *J Am Med Assoc* 143: 329–336, 1950. doi:[10.1001/jama.1950.02910390001001](https://doi.org/10.1001/jama.1950.02910390001001).
 16. **Wynder EL, Graham EA, Croninger AB.** Experimental production of carcinoma with cigarette tar. *Cancer Res* 13: 855–864, 1953.

