

VIEWPOINT

Flavorings in Electronic Cigarettes

An Unrecognized Respiratory Health Hazard?

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Use of electronic cigarettes (e-cigarettes), vape pens, e-hookah, e-cigars, e-pipes, or other electronic nicotine delivery systems (ENDS) has increased rapidly since their introduction in the United States in 2007, growing to a \$2 billion market.¹ There is controversy concerning the utility of ENDS as a harm reduction strategy, reflecting major gaps in the emerging evidence on potential benefits and harms of the products.²⁻⁴ Although exclusive use of ENDS is generally considered to be less risky for individuals than smoking combustible tobacco products, there is concern that their availability may both lead to dual product use (ie, ENDS and cigarettes) and reduce cessation. Additionally, there is concern that ENDS may be used by nonsmoking adolescents and young adults who might not otherwise have used nicotine-delivering products, and that dual use may follow. Numerous flavored products that have seeming appeal to adolescents and young adults are on the market, such as Cherry Crush, Chocolate Treat,

flavors or by using flavoring available directly from food flavoring manufacturers to create unique flavors.

Flavorings are a largely unrecognized potential hazard of ENDS, which are designed to create an ultrafine aerosol that penetrates deeply into the lungs. Respiratory toxins in flavorings thus may pose a threat to the respiratory health of users. The Flavor and Extract Manufacturers Association evaluates the safety of chemicals used in food flavorings, many of which also may be used in ENDS. However, the association's research is limited to the evaluation of the safety of chemicals in food (for ingestion), and as such, ENDS flavorings using the same chemicals cannot be also be deemed "generally recognized as safe" for inhalation.⁵ For example, the chemical diacetyl (2,3-butanedione) is used to give foods a buttery or creamy flavor. High doses of diacetyl, deemed safe for ingestion by the Flavor and Extract Manufacturers Association and the US Food and Drug Administration (FDA), have been shown to cause acute-onset bronchiolitis obliterans, a severe and irreversible obstructive lung disease, when inhaled by workers exposed to particulate aerosolized flavorings containing diacetyl. Bronchiolitis obliterans was originally recognized as "popcorn lung" in an outbreak among flavor manufacturing workers at a microwave popcorn production plant, caused by inhalation of diacetyl in popcorn butter flavorings.⁶

Research is needed to characterize both the presence of toxic chemicals in ENDS flavorings and the potential adverse respiratory effects of exposure to e-liquids, especially flavorings.

Snappin' Apple, and Vanilla Dreams flavors; their availability may generate an entirely new population of nicotine-addicted users among never-users of combustible tobacco products.

Given the limited timespan over which these products have been in the marketplace, the long-term safety of ENDS is uncertain. One concern that has received little attention is the potential for toxic effects from inhaled flavorings. To date, research on pulmonary toxicity has focused largely on the nicotine-containing solution (e-liquid) vaporized by ENDS, composed in most products of some combination of propylene glycol, vegetable glycerin, nicotine, and flavorings.² Recent *in vitro* studies found that the cytotoxic effects of e-liquids were largely restricted to flavoring components.² The diversity of ENDS products, in particular of flavorings, is also increasing at a rapid rate. As of January 2014, there were 466 distinct brands of electronic nicotine products and at least 7764 unique flavors, an increase of about 10.5 brands and 242 new flavor products per month from August 2013 to January 2014.¹ In addition, many users may create their own mixtures of flavorings by combining different

There is currently no enforceable workplace standard specific to diacetyl. The National Institute for Occupational Safety and Health at the Centers for Disease Control and Prevention has recommended an 8-hour time-weighted occupational exposure limit of 5 ppb. In light of research on the adverse effects of diacetyl inhalation, other diketone flavorings (eg, 2,3-pentanedione, 2,3-hexanedione, and 2,3-heptanedione) have been used as flavoring substitutes for diacetyl. However, some research suggests that these diketone substitutes may be as toxic to the lung as diacetyl.⁷ A recent evaluation of 159 sweet-flavored ENDS solutions found diacetyl in 69.2% of samples and in at least 1 sample from 92% of manufacturers⁸; 2,3-pentanedione was found in one-third of samples. The investigators estimated the daily inhaled exposure to diacetyl and 2,3-pentanedione among users of 3 mL per day of ENDS refill solution (or diluted flavoring solution), and concluded that 47.3% of diacetyl- and 41.5% of 2,3-pentanedione-containing solutions resulted in exposures exceeding the National Institute for Occupational Safety and Health-recommended standard.⁸

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The potential hazards of ENDS flavorings are not limited to diacetyl and its substitutes. Flavorings may also contain other chemicals used in food flavorings that are considered safe for ingestion but not for inhalation. In 2012, the Flavor and Extract Manufacturers Association issued a report that lists 27 high-priority flavoring substances to be evaluated for permissible respiratory exposure limits in the workplace, based on adverse respiratory toxic effects. These included diacetyl and diacetyl substitutes, and other chemicals that may be added to ENDS or may be by-products of the manufacturing process.⁹ The potential for respiratory effects in ENDS users is of concern to the association, which recently released a reminder that the primary safety assessment programs for flavors are restricted to flavorings used in human foods, and that "e-cigarette manufacturers should not represent or suggest that the flavor ingredients used in their products are safe because they have FEMA [Flavor and Extract Manufacturers Association] 'generally recognized as safe' status for use in food because such statements are false and misleading."⁵

ENDS online user groups have also expressed concern about the potential health effects of diacetyl in flavorings. However, the potential respiratory hazards of flavorings are largely absent from the public health and regulatory agenda, which has primarily focused on the use of flavors to appeal to youth as part of aggressive industry marketing, and the resulting risk of nicotine addiction in adolescent populations. A recent position statement on ENDS by the Forum of International Respiratory Societies contained one line on

the potential hazards of flavorings. To our knowledge, there has only recently been one published analysis of diacetyl and 2,3-pentanedione in ENDS flavorings and little analysis of other potential respiratory toxins, and there has not been sufficient time to conduct an epidemiologic study to understand the association between use of ENDS flavorings and adverse respiratory health effects in human populations.

At present, there is no jurisdiction to regulate the composition of e-liquids, no regulatory program to assess the hazards of the flavorings in ENDS products, and no surveillance system in place to identify ENDS users with severe respiratory disease. The proposed Deeming Regulations of the FDA, which would extend the agency's authority to regulate products meeting the statutory definition of "tobacco products" (including ENDS), only propose to restrict the sale of flavored ENDS to minors. There is no proposed regulation of the composition of ENDS flavorings based on respiratory health effects, in part due to the lack of available research on the toxic and adverse health effects of ENDS flavorings. Research is needed to characterize both the presence of toxic chemicals in ENDS flavorings and the potential adverse respiratory effects of exposure to e-liquids, especially flavorings. In the meantime, regardless of the potential long-term harm reduction benefits of ENDS, an important policy question is whether the still uncertain risk of potentially serious lung disease merits precautionary regulation of e-liquid composition in the face of considerable scientific uncertainty.

ARTICLE INFORMATION

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REFERENCES

- Zhu SH, Sun JY, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control*. 2014;23(suppl 3):iii3-iii9.
- Grana R, Benowitz N, Glantz SA. e-Cigarettes: a scientific review. *Circulation*. 2014;129(19):1972-1986.
- Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA*. 2014;311(2):135-136.
- Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet*. 2013;382(9905):1629-1637.
- Hallagan J. The safety assessment and regulatory authority to use flavor—focus on e-cigarettes. <http://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-e-cigarettes>. Published May 2014. Accessed November 7, 2014.
- Kreiss K. Work-related spirometric restriction in flavoring manufacturing workers. *Am J Ind Med*. 2014;57(2):129-137.
- Potera C. Still searching for better butter flavoring. *Environ Health Perspect*. 2012;120(12):A457.
- Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins [published online September 1, 2014]. *Nicotine Tob Res*. doi: 10.1093/ntr/ntu176.
- Respiratory Health and Safety in the Flavor Manufacturing Workplace: 2012 Update*. Washington, DC: The Flavor and Extract Manufacturers Association of the United States; 2012.