

Safety Assessment and Regulatory Authority to Use Flavors: Focus on Electronic Nicotine Delivery Systems and Flavored Tobacco Products

First posted May 2013

Revised September 2018

The Use of Flavors in ENDS and Flavored Tobacco Products

“Electronic nicotine delivery systems” (ENDS), including “electronic cigarettes” (“e-cigarettes”), provide the means by which the user inhales vapor from a mixture of constituents typically including nicotine, flavor and other materials. The use of ENDS, and other flavored non-cigarette tobacco products like cigars, smokeless tobacco products, and hookah products is increasing. The 2009 Family Smoking Prevention and Tobacco Control Act prohibits the use of “characterizing flavors,” except for tobacco flavors and menthol, in combustible cigarettes but not in other tobacco products such as cigars and smokeless tobacco products, or in hookah smoking products (“flavored tobacco products”). There are several important issues associated with the use of flavors in ENDS, and other flavored tobacco products.

1. There is no apparent direct regulatory authority in the United States to use flavors in ENDS, and flavored tobacco products. In this context, it is important to note that the “generally recognized as safe” (GRAS) provision in Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FFDCA) applies only to food as defined in Section 201(f) of the Act.
2. None of the primary safety assessment programs for flavors, including the GRAS program sponsored by the Flavor and Extract Manufacturers Association of the United States (FEMA), evaluate flavor ingredients for use in products other than human food. FEMA GRAS™ status for the use of flavor ingredients in food does not provide regulatory authority to use flavor ingredients in ENDS, or any tobacco products in the U.S.
 - The manufacturers and marketers of ENDS, and all other flavored tobacco products, and flavor manufacturers and marketers, should not represent or suggest that the flavor ingredients used in these products are safe because they have FEMA GRAS™ status for use in food because such statements are false and misleading.
 - The manufacturers and marketers of ENDS, and all other flavored tobacco products should take appropriate action to assure the safety of flavor ingredients used in these products. FEMA GRAS™ status for the use of flavor ingredients in food does not mean that FEMA GRAS™ flavor ingredients are safe for use in ENDS and flavored tobacco products.

3. The U.S. Food and Drug Administration (FDA) has been concerned with issues associated with ENDS for some time. In 2010 FDA issued [regulatory correspondence on e-cigarettes](#). In 2014, FDA published proposed regulations to deem ENDS, cigars, hookah tobacco, pipe tobacco, and certain other products as tobacco products subject to the regulatory authority of the 2009 Family Smoking Prevention and Tobacco Control Act amendments to the Federal Food, Drug, and Cosmetic Act thereby bringing them under regulation by the FDA. [80 Fed. Reg. 23142 \(25 April 2014\)](#). FDA's final rule deeming ENDS to be tobacco products subject to the Act was published in 2016. [81 Fed. Reg. 28974. 10 May 2016](#).

Although the final deeming rule did not prohibit the use of flavors in these products, FDA designated flavors as “components” of ENDS and explained that the agency intended to consider a proposed tobacco product standard that would prohibit characterizing flavors in deemed tobacco products, including ENDS. On March 21, 2018, FDA took its first step to consider such regulatory action by publishing an Advanced Notice of Proposed Rulemaking (ANPR) seeking information from stakeholders on the role flavors play in tobacco products. [83 Fed. Reg. 12294. 21 Mar. 2018](#). FDA's ANPR reflects the agency's primary concern about the increase in the use of flavored tobacco products, including ENDS, among American youth. [FEMA submitted comments on FDA's ANPR](#) reiterating its long-standing positions on the safety assessment and regulatory authority to use flavors in deemed tobacco products.

In September 2018, [FDA Commissioner Gottlieb issued an extensive statement](#) on the direction of FDA's policies on regulating e-cigarettes noting that the agency has also issued a series of [warning letters](#) to the manufacturers of e-cigarettes and their components.

The Regulation of Flavors in the United States

In the U.S., the vast majority of flavoring substances are added to food consistent with the GRAS provision in FFDCa Section 201(s). For the purposes of the FFDCa GRAS provision, food is defined in FFDCa Section 201(f) as “(1) articles used for food or drink for man or other animals, (2) chewing gum, (3) articles used as components for any such article.” The primary route to regulatory authority to use flavor ingredients in the U.S. is the FEMA GRAS™ program.

The FEMA Expert Panel

The FEMA Expert Panel evaluates the safety of flavoring substances only under their conditions of intended use in human food, including beverages and chewing gum. Therefore, the Expert Panel only evaluates flavor ingredients for exposure through ingestion. The Expert Panel does not evaluate flavor ingredients for use in ENDS or any tobacco products, or other products that are not human food, or products that result in exposures other than by ingestion.

Other Safety Assessment and Regulatory Programs

There are a variety of programs in various countries and geographic regions to evaluate the safety of flavoring substances for use in food. All of these programs evaluate the safety of flavoring substances only under their conditions of intended use in human food meaning that they are evaluated only for safety upon ingestion. In Europe, flavoring substances are evaluated by the European Food Safety Authority solely for their use in human food. Also consistent with this principle is the global

flavor safety evaluation program conducted by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) that also evaluates the safety of flavoring substances solely for their use in human food.

Occupational Exposure Limits and E-Cigarettes

Occupational exposure limits (OELs) have been established for a small number of flavoring substances. OELs have no relevance to exposure to flavors from the use of ENDS or other uses that do not constitute exposure in the workplace. OELs, such as permissible exposure limits (PELs) established by the Occupational Safety and Health Administration (OSHA), recommended exposure limits (RELs) established by the National Institute for Occupational Safety and Health (NIOSH) and threshold limit values (TLVs) established by the American Conference of Government Industrial Hygienists (ACGIH), are intended to serve as regulatory limits in the case of OSHA PELs, or in the case of RELs and TLVs, as benchmarks for limiting exposure to substances in the workplace. It is improper to use OELs as indications of safe levels of exposure to flavoring substances from the use of ENDS and exposures that do not occur in the workplace.

Recent Publications of Interest

Allen J.G., Flanigan S.S., LeBlanc M., Vallarino J., MacNaughton P., Stewart J.H. and Christiani D.C. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environmental Health Perspectives*. 124, 733. 2016.

Behar R.Z., Wentai L., McWhirter K.J., Pankow J.F., and Talbot P. Analytical and toxicological evaluation of flavor chemicals in electronic cigarette refill fluids. *Scientific Reports*. May 29, 2018. Available at <https://www.nature.com/articles/s41598-018-25575-6>.

Farley S.M., Schroth K.R., Grimshaw V., Luo W., DeGagne J.L., Tierney P.A., Kim K., and Pankow J.F. Flavor chemicals in a sample of non-cigarette tobacco products without explicit flavor names sold in New York City in 2015. *Tobacco Control*. 27, 170. 2018.

Fetterman J.I., Weisbrod R.M., Feng B., Bastin R., Tuttle S.T., Holbrook M., Baker G., Roberson R.M., Conklin D.J., Bhatnagar A., and Hamburg N.M. Flavorings in tobacco products induce endothelial cell dysfunction. *Arteriosclerosis, Thrombosis, and Vascular Biology*. 7. 2018.

Khan M., Khateeb F.M., Khan Z., Akhtar J., Srouf K, and Hammersley J.R. A case of organizing pneumonia related to electronic cigarette use. Abstract. American Thoracic Society International Conference. May 2018.

Macedonia T.V., Krefft S.D. and Rose C.S. Severe fixed obstructive lung disease in a former smoker with heavy e-cigarette use. Abstract. American Thoracic Society International Conference. May 2018.

National Academies of Sciences, Engineering and Medicine. Public health consequences of e-cigarettes. The National Academies Press. Available at <http://nap.edu/24952>. 2018.

Poponea N., Shehada E., and Freeman N. The dark side of vaping: acute dyspnea and granulomatous lung disease associated with electronic cigarettes. Abstract. American Thoracic Society International Conference. May 2018.

Russell C., McKeganey N., Dickson T., and Nides, M. Changing patterns of first e-cigarette flavor used and current flavors used by 20,836 adult frequent e-cigarette users in the USA. *Harm Reduction Journal*. 15. 2018.

Sommerfeld, C.G., Weiner D.J., Nowalk A., and Larkin A. Hypersensitivity pneumonitis and acute respiratory distress syndrome from e-cigarette use. *Pediatrics*. 141, 6. 2018.

Staudt M.R., Salit J., Kaner R.J., Hollmann C., and Crystal R.G. Altered lung biology of healthy never smokers following acute inhalation of e-cigarettes. *Respiratory Research*. 19, 78. 2018.

Tzortzi A., Teloniatis S.I., Matiampa G., Bakelas G., Vyzikidou V.K., Vardavas C., Behrakis P.K. and Fernadez E. Passive exposure to e-cigarette emissions: Immediate respiratory effects. *Tobacco Prevention & Cessation*. 4, 18. 2018.

Zhu S.-H., Sun J.Y., Bonnevie E., Cummins S.E., Gamst A., Yin L., and Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tobacco Control*. 23, iii3. 2016.

Zwack L.M., Stefaniak AS.B., and LeBouf R.F. Evaluation of chemical exposures at a vape shop. NIOSH Health Hazard Evaluation Program. HHE Report 2015-0107-3279. 2018.

For More Information

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