

In addition to the three constituents FDA proposes to add to the newly expanded list of Harmful and Potentially Harmful Constituents, FDA should also add cinnamaldehyde, vanillin, ethyl vanillin, and cooling agents such as WS-3 and WS-23 which are frequently found in e-cigarettes and other ENDS products

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for “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List Additions and Request for Comments.”

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We applaud FDA’s decision¹ to add 18 new constituents to the list of Harmful and Potentially Harmful Constituents (HPHC). These additions reflect the more current range of tobacco and nicotine products under FDA’s jurisdiction and the dangers associated with the chemicals and chemical compounds that are ingredients in these products.

We strongly support FDA’s proposal to add three other constituents to the list that are often added to e-liquid formulations as flavors – pulegone, furfuryl alcohol, and methyl eugenol. A 2022 review of high impact published papers studying the toxicological harms associated with e-cigarettes provides growing evidence of the toxicological risks associated with e-cigarette use. These risks include DNA damage that increases cancer risk due to the presence of several carcinogenic chemical compounds found in e-cigarette emissions, increased risk of pulmonary and cardiovascular disease, and impairment of male fertility. In particular, aldehydes in flavoring agents affect cytochrome P450 2A6, which is involved in the oxidative metabolism of nicotine.² A recent 2026 review of peer-reviewed literature since 2017 involving a qualitative carcinogenic risk assessment of nicotine-based e-cigarettes highlights the carcinogenicity of e-cigarettes. The review concludes with a “clear and authoritative assessment” that “e-cigarettes delivering nicotine are likely to be carcinogenic to humans who use them causing oral cancer and lung cancer,” and this cancer burden is separate from cancer attributable to e-cigarette users who

¹ Food and Drug Administration, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List Additions and Request for Comments. 91 FR 21824 (April 23, 2026).

² Vivarelli F, Granata S, Rullo L et al. On the toxicity of e-cigarettes consumption: focus on pathological cellular mechanisms. *Pharmacol Res* 2022;182:106315.

transition to smoking and dual use.³ As detailed below, we enthusiastically support FDA’s proposal to add these three constituents to the HPHC list.

We also suggest that FDA add cinnamaldehyde, vanillin, ethyl vanillin, and cooling agents such as WS-3 and WS-23 to the HPHC list.

1. FDA should add pulegone to the HPHC list

We strongly support FDA’s proposal to add pulegone to the HPHC list. We suggested adding pulegone to the HPHC list in the public comment we submitted to the August 2019 docket⁴ (attached and incorporated by reference). Pulegone, a constituent of oil extracts prepared from mint plants, is a carcinogen that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms in rodents, and can also cause liver and kidney failure. Pulegone in e-liquids is a concern because of its known carcinogenicity.⁵ Although the FDA banned synthetic pulegone as a food additive in 2018⁶ and the chemical is banned in the European Union and in the state of California, substantial amounts of pulegone have been detected in mint- and menthol-flavored e-cigarette liquids⁷ and smokeless tobacco products. Jabba and Jordt’s September 2019 analysis⁸ measured daily pulegone exposure from e-cigarettes and smokeless tobacco at higher levels compared with exposure from menthol cigarettes and compared the risk associated with pulegone content in combustible menthol cigarettes to the pulegone content in mint- and menthol-flavored e-cigarettes and smokeless tobacco.

The margin of exposure (MOE) is the measure used by the FDA and other regulatory agencies for cancer risk assessment of food additives, and cancer risk is inversely proportional to the MOE, with values of 10,000 or below requiring mitigation strategies. This study found that the MOE for all the products that were analyzed are below the accepted MOE threshold of 10,000 for carcinogens. This suggests that users of mint- and menthol-flavored e-cigarettes and smokeless tobacco are exposed to pulegone levels higher than the FDA considers unacceptable

³ Stewart BW, Marshall H, Bonevski B, Griffin HJ, Hopkins AM, Itchins M, Mazza CJ, Modi ND, Ryan M, Varlow M, Sitas F. The carcinogenicity of e-cigarettes: a qualitative risk assessment. *Carcinogenesis*. 2026;47: 1-14 doi: 10.1093/carcin/bgag015. PMID: 41910510.

⁴ Lempert LK, St.Helen G, Gotts J, et al. In addition to the 19 constituents FDA proposes to add to the list of Harmful and Potentially Harmful Constituents, FDA should also add compounds that may be carcinogenic or cause pulmonary or cardiovascular harms when inhaled, especially oils and chemicals and chemical classes found in e-cigarette flavorants, and FDA should use as additional criteria California’s Proposition 65 list of **carcinogens and reproductive toxicants** and the California Air Resources Board’s list of Toxicant Air Contaminants. (October 2, 2019). <https://www.regulations.gov/comment/FDA-2012-N-0143-0037>

⁵ National Toxicology Program. Toxicology and carcinogenesis studies of pulegone Cas No. 89–82–7) in f344/n rats and B6C3F1 mice (gavage studies). *Natl. Toxicol. Program Technol. Rep. Ser* 2011;563:1–201.

⁶ United States Food and Drug Administration. Food additive regulations; synthetic flavoring agents and adjuvants. *Federal Register* 2018;83:50490–503 <https://www.federalregister.gov/documents/2018/10/09/2018-21807/food-additive-regulations-synthetic-flavoring-agents-and-adjuvants>

⁷ Omaiye EE, Luo W, McWhirter KJ, et al. Electronic cigarette refill fluids sold worldwide: flavor chemical composition, toxicity, and hazard analysis. *Chem Res Toxicol* 2020;33:2972–87.

⁸ Jabba SV, Jordt S. Risk analysis for the carcinogen pulegone in Mint- and Menthol- Flavored e- cigarettes and smokeless tobacco products. *JAMA Intern Med* 2019;179:1721–3.

for intake of synthetic pulegone in food, and higher than in smokers of combustible menthol cigarettes. Omaiye's 2019 study⁹ found that mint-, menthol-, and cucumber-flavored Juul pods, not studied in the Jabba/Jordt analysis, also contain pulegone. Mint oil used to flavor many e-liquids usually contains pulegone. Omaiye's 2022 study¹⁰ found that pulegone concentrations in mint products from Juul and Puff Bar were high enough to present a cancer risk based on MOE evaluations.

Because these findings establish health risks associated with pulegone intake, especially in connection with use of mint- and menthol-flavored e-cigarettes and smokeless tobacco, FDA should add pulegone to the list of HPHCs.

2. FDA should add furfuryl alcohol to the HPHC list

We support FDA's proposal to add furfuryl alcohol to the HPHC list. Furfuryl alcohol is a known IARC class 2B carcinogen¹¹ known to induce kidney tumors in mice.^{12, 13} It is a known respiratory irritant, and can be converted to a genotoxin when inhaled.¹⁴ Cigarette smoke, waterpipe, and e-cigarette aerosol may be sources of inhalation exposure. Of particular concern, furfuryl alcohol has been detected in flavored unburned waterpipe tobacco at ~ 2 µg/g, and is 31 times more concentrated in waterpipe tobacco smoke than cigarette smoke. Additionally, its sweet caramel and coffee aroma may enhance the appeal of waterpipe tobacco smoke making it easier to initiate and continue use. Therefore, furfuryl alcohol potentially increases both the direct and indirect harms from waterpipe smoking.^{15, 16}

3. FDA should add methyl eugenol to the HPHC list

⁹ Omaiye E, McWhirter K, Luo W, et al., High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations. *Chemical Research in Toxicology* 2019 32(6), 1058-1069

¹⁰ Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Flavour chemicals, synthetic coolants and pulegone in popular mint-flavoured and menthol-flavoured e-cigarettes. *Tobacco control*. 2022 Aug 1;31(e1):e3-9.

¹¹ International Agency for Research on Cancer (IARC), IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 119. Some chemicals that cause tumours of the urinary tract in rodents. Feb. 20, 2019. <https://publications.iarc.who.int/575>

¹² Glatt H, Meinel W. Sulphotransferase-mediated toxification of chemicals in mouse models: effect of knockout or humanisation of SULT genes. *Essays Biochem*. 2024 Dec 4;68(4):523-539. doi: 10.1042/EBC20240030. PMID: 39611595; PMCID: PMC11625864.

¹³ National Toxicology Program. Toxicology and Carcinogenesis Studies of Furfuryl Alcohol (CAS No. 98-00-0) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). *Natl Toxicol Program Tech Rep Ser*. 1999;482:1-248.

¹⁴ Monien BH, Sachse B, Meinel W, Abraham K, Lampen A, Glatt H. Hemoglobin adducts of furfuryl alcohol in genetically modified mouse models: Role of endogenous sulfotransferases 1a1 and 1d1 and transgenic human sulfotransferases 1A1/1A2. *Toxicology letters*. 2018 Oct 1;295:173-8.

¹⁵ Brinkman MC, Kim H, Buehler SS, Adetona AM, Gordon SM, Clark PI. Evidence of compensation among waterpipe smokers using harm reduction components. *Tobacco control*. 2018 Oct 30;tobaccocontrol-2018.

¹⁶ Wagener TL, Leavens ELS, Mehta T, Hale JJ, Shihadeh A, Eissenberg T, Halquist MS, Brinkman MC, Johnson AL, Floyd EL, Ding K. Impact of Flavors and Sweeteners on Waterpipe Tobacco Smoking Topography, Abuse Liability, Toxicant Exposure, and Intentions for Continued Use. Draft planned for submission to Tobacco Control.

We support FDA’s proposal to add methyl eugenol to the HPHC list. In 2018, the FDA amended its food additive regulations and removed authorization for use of synthetic methyl eugenol as a food flavoring additive based on studies showing they induce cancer in animal studies.¹⁷ Although prohibited in foods, methyl eugenol is a flavor and fragrance compound that is found in many tobacco products with clove or fruit flavoring including bidi cigarettes, kreteks, e-liquids, oral nicotine pouches, and some conventional cigarettes.¹⁸ The National Toxicology Program determined in 2021 that methyl eugenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.¹⁹ Methyl eugenol was identified as an ingredient in nicotine pouches in a 2023 toxicology study.²⁰ In 2023, the International Agency for Research on Cancer (IARC) classified methyl eugenol the as *probably carcinogenic to humans*.^{21, 22}

4. In addition to the additional three constituents FDA proposed, FDA should also add cinnamaldehyde, vanillin, ethyl vanillin, and cooling agents such as WS-3 and WS-23 to the HPHC list

a. Flavor additives that are “Generally Recognized as Safe” (GRAS) by the FDA when ingested as food does not mean they are safe when inhaled in tobacco and nicotine products

As a starting point, FDA must acknowledge and act on the fact that while some flavors (e.g., vanilla and cinnamon) that are flavor additives in food products have been “Generally Recognized as Safe” (GRAS) by the FDA for ingestion, this does not mean they are not safe when inhaled in e-cigarettes or other devices. GRAS is a provision within the definition of a food additive under 21 USC 321(s) and as such, the safety of foods designated as “GRAS” is based on oral consumption (i.e., eaten or ingested as a food), and cannot serve as an indicator of the toxicity or safety of e-cigarette ingredients when aerosolized and inhaled. A 2024 review of the toxicity of ingredients in e-cigarettes, including those ingredients that have been determined to be GRAS in food, describes the potentially significant harms associated with inhalation or cell exposure when several substances listed as GRAS in food are used in e-cigarettes via proinflammatory effects as well as immune suppression, respiratory tract irritation, and cytotoxicity.²³ The 15 substances described in a 2024 review are: acetaldehyde, acetoin,

¹⁷ US Food and Drug Administration. FDA Removes 7 Synthetic Flavoring Substances from Food Additives List. October 5, 2018. <https://www.fda.gov/food/hfp-constituent-updates/fda-removes-7-synthetic-flavoring-substances-food-additives-list>

¹⁸ National Library of Medicine, Methyleugenol. <https://www.ncbi.nlm.nih.gov/books/NBK373178/>

¹⁹ National Toxicology Program. 15th Report on Carcinogens [Internet]. Research Triangle Park (NC): National Toxicology Program; 2021 Dec 21. Methyleugenol: CAS No. 93-15-2. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK590859/>

²⁰ Mallock-Ohnesorg N, Rinaldi S, Malke S, et al. Oral nicotine pouches with an aftertaste? Part 1: screening and initial toxicological assessment of flavorings and other ingredients. Arch Toxicol. 2023;97(9):2357-2369. doi:10.1007/s00204-023-03538-9

²¹ Riboli E, Beland FA, Lachenmeier DW, et al. Carcinogenicity of aspartame, methyleugenol, and isoeugenol. Lancet Oncol. 2023;24(8):848-850. doi:10.1016/S1470-2045(23)00341-8

²² International Agency for Research on Cancer (IARC). IARC Monographs on the Identification of Carcinogenic Hazards to Humans, Volume 134. Aspartame, Methyleugenol, and Isoeugenol. April 29, 2024.

²³ Kassem, N.O.F.; Strongin, R.M.; Stroup, A.M.; Brinkman, M.C.; El-Hellani, A.; Erythropel, H.C.; Etemadi, A.; Exil, V.; Goniewicz, M.L.; Kassem, N.O.; et al. A Review of the Toxicity of Ingredients in e-Cigarettes, Including

cinnamaldehyde, diacetyl, ethyl acetate, eugenol, tocopherol acetate, triacetin, linalool, benzaldehyde, carvone, decanal, ethyl butyrate, ethyl vanillin, limonene.²⁴

The Flavor and Extract Manufacturers Association (FEMA) Expert Panel that recommends compounds for GRAS designation evaluates the safety of flavor ingredients only under their conditions of intended use in food and only for exposure through ingestion. FEMA does not evaluate flavor ingredients for use in tobacco products including e-cigarettes or any products that result in exposures other than by ingestion. “Therefore, FEMA GRAS status for the use of a flavor ingredient in food does not provide regulatory authority to use the flavor ingredient in e-cigarettes, ENDS devices or other tobacco products in the U.S.”²⁵ Further, FEMA referred to its “long-standing statement²⁶ that flavor ingredients are not evaluated by the FEMA Expert Panel for safety and GRAS status for any uses other than use in food (<https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-electronic-nicotine-delivery-systems>). Therefore, use in ENDS and other tobacco products must have separate safety assessments to assure safety and establish regulatory authority to use flavors in such products.”²⁷

The American Thoracic Society similarly noted that GRAS applies to ingested and stated: “We note that much of the tobacco, vaping and e-cigarette industry state that the flavoring ingredients used in tobacco products are GRAS. While it may be true these products are GRAS in the digestive tract, ***these products have not been tested in the respiratory system and their safety in the respiratory tract is unknown.*** This point has been made frequently by representatives of the flavoring industry.”²⁸

b. The flavor additives cinnamaldehyde, vanillin and ethyl vanillin should be added to the HPHC list

The flavor additives cinnamaldehyde, vanillin and ethyl vanillin are frequently ingredients in e-cigarettes, other ENDS, and other tobacco products. ***Because they are associated with significant toxicity and harmful effects when inhaled, regardless of whether they have been designated as GRAS for ingestion in food, these flavor additives should be added to the HPHC list.***

Cinnamon-flavored ENDS were known to be highly toxic since at least 2014.²⁹ Cinnamaldehyde is the major flavor chemical in cinnamon flavored e-liquids, and cinnamon-

Those Ingredients Having the FDA’s “Generally Recognized as Safe (GRAS)” Regulatory Status for Use in Food. *Nicotine Tob. Res.* 2024, 26, 1445–1454.

²⁴ Kassem, N.O.F.; Strongin, R.M.; Stroup, A.M.; Brinkman, M.C.; El-Hellani, A.; Erythropel, H.C.; Etemadi, A.; Exil, V.; Goniewicz, M.L.; Kassem, N.O.; et al. A Review of the Toxicity of Ingredients in e-Cigarettes, Including Those Ingredients Having the FDA’s “Generally Recognized as Safe (GRAS)” Regulatory Status for Use in Food. *Nicotine Tob. Res.* 2024, 26, 1445–1454.

²⁵ <https://www.regulations.gov/comment/FDA-2012-N-0143-0055>

²⁶ <https://www.femaflavor.org/sites/default/files/2018-05/FEMAGRAS%20Ecig%2004302018.pdf>

²⁷ <https://www.regulations.gov/comment/FDA-2012-N-0143-0055>

²⁸ <https://www.regulations.gov/comment/FDA-2012-N-0143-0041>

²⁹ Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro.* 2014;28(2):198–208. doi: 10.1016/j.tiv.2013.10.006. PubMed PMID: 24516877.

flavored e-liquids such as “Atomic Cinnacide” and “Cinnamon Fireball” contain more than 10% of toxic cinnamaldehyde. It is well established that cinnamaldehyde, an ingredient in cinnamon e-cigarettes, is dangerous for anyone to inhale.^{30, 31} Toxicological studies published over the last 12 years have consistently demonstrated the toxicity of cinnamaldehyde and cinnamon-flavored ENDS.^{32, 33, 34, 35, 36, 37, 38, 39, 40, 41}

³⁰ Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, Jaspers I. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am J Physiol Lung Cell Mol Physiol*. 2017 Aug 1;313(2):L278-L292. doi: 10.1152/ajplung.00452.2016. Epub 2017 May 11. PMID: 28495856; PMCID: PMC5582929

³¹ Behar RZ, Luo W, Lin SC, et al. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob Control*. Nov 2016;25(Suppl 2):ii94-ii102. doi:10.1136/tobaccocontrol-2016-053224

³² Behar RZ, Luo W, Lin SC, Wang Y, Valle J, Pankow JF, Talbot P. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. *Tob Control*. 2016;25(Suppl 2):ii94-ii102. Epub 20160915. doi: 10.1136/tobaccocontrol-2016-053224. PubMed PMID: 27633763; PMCID: PMC5503843.

³³ Effah F, Elzein A, Taiwo B, Baines D, Bailey A, Marczylo T. In Vitro high-throughput toxicological assessment of E-cigarette flavors on human bronchial epithelial cells and the potential involvement of TRPA1 in cinnamon flavor-induced toxicity. *Toxicology*. 2023;496:153617. Epub 20230817. doi: 10.1016/j.tox.2023.153617. PubMed PMID: 37595738.

³⁴ Raduka A, Gao N, Chatburn RL, Rezaee F. Electronic cigarette exposure disrupts airway epithelial barrier function and exacerbates viral infection. *Am J Physiol Lung Cell Mol Physiol*. 2023;325(5):L580-193. Epub 20230912. doi: 10.1152/ajplung.00135.2023. PubMed PMID: 37698113; PMCID: PMC11068398.

³⁵ Bengalli R, Ferri E, Labra M, Mantecca P. Lung Toxicity of Condensed Aerosol from E-CIG Liquids: Influence of the Flavor and the In Vitro Model Used. *Int J Environ Res Public Health*. 2017;14(10). Epub 20171020. doi: 10.3390/ijerph14101254. PubMed PMID: 29053606; PMCID: PMC5664755.

³⁶ Clapp PW, Lavrich KS, van Heusden CA, Lazarowski ER, Carson JL, Jaspers I. Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(3):L470-186. Epub 20190103. doi: 10.1152/ajplung.00304.2018. PubMed PMID: 30604630; PMCID: PMC6459291.

³⁷ Noël A, Hansen S, Zaman A, Perveen Z, Pinkston R, Hossain E, Xiao R, Penn A. In utero exposures to electronic-cigarette aerosols impair the Wnt signaling during mouse lung development. *Am J Physiol Lung Cell Mol Physiol*. 2020;318(4):L705-122. Epub 20200221. doi: 10.1152/ajplung.00408.2019. PubMed PMID: 32083945.

³⁸ Cahill KM, Gartia MR, Sahu S, Bergeron SR, Heffernan LM, Paulsen DB, Penn AL, Noël A. In utero exposure to electronic-cigarette aerosols decreases lung fibrillar collagen content, increases Newtonian resistance and induces sex-specific molecular signatures in neonatal mice. *Toxicol Res*. 2022;38(2):205-24. Epub 20210906. doi: 10.1007/s43188-021-00103-3. PubMed PMID: 35415078; PMCID: PMC8960495.

³⁹ Noël A, Johnson T, Schexnayder M, Xiao R, Langohr I, Penn A. Altered lung function in mice is a sensitive indicator of lung damage following 6 months of electronic nicotine delivery system aerosol exposure. *Am J Physiol Lung Cell Mol Physiol*. 2026;330(5):L487-1503. Epub 20260319. doi: 10.1152/ajplung.00209.2025. PubMed PMID: 41855091; PMCID: PMC13089630.

⁴⁰ Christian N, Burden D, Emam A, Brenk A, Sperber S, Kalu M, Cuadra G, Palazzolo D. Effects of E-Liquids and Their Aerosols on Biofilm Formation and Growth of Oral Commensal Streptococcal Communities: Effect of Cinnamon and Menthol Flavors. *Dent J (Basel)*. 2024;12(8). Epub 20240723. doi: 10.3390/dj12080232. PubMed PMID: 39195076; PMCID: PMC11353068.

⁴¹ Aragón-Gutiérrez A, Heras-Mozos R, Gallur M, López D, Gavara R, Hernández-Muñoz P. Hot-Melt-Extruded Active Films Prepared from EVOH/Trans-Cinnamaldehyde Blends Intended for Food Packaging Applications. *Foods*. 2021;10(7). Epub 20210708. doi: 10.3390/foods10071591. PubMed PMID: 34359460; PMCID: PMC8304191.

In addition to cinnamaldehyde, other flavor aldehydes including vanillin and ethyl vanillin react with the e-liquid solvent propylene glycol (PG), are chemically unstable and convert to flavor aldehyde PG acetals that are inhaled by the user with toxicological effects.⁴² Toxic aldehydes are produced by e-cigarettes with both flavored and “unflavored” e-liquids, but decomposition of flavoring compounds is the main source of the emitted toxic aldehydes, and thermal decomposition of flavoring compounds during vaping produces levels that exceed occupational safety standards.⁴³ This is concerning because FDA suggested in its draft guidance on considerations related to youth risk of flavored ENDS premarket applications that “spice” flavors, which would include cinnamon- and vanilla-flavored e-cigarettes, may have lower youth appeal so therefore FDA would require less evidence of adult benefits. Mechanistic studies of cinnamaldehyde found this chemical impairs respiratory cell immune function,⁴⁴ and induces mitochondrial dysfunction and cellular stress responses in kidney cells,⁴⁵ and produces formaldehyde and acetaldehyde when heated.⁴⁶ Studies of aerosolized flavors in e-cigarettes including cinnamaldehyde, vanillin, and ethyl vanillin found negative effects on cardiac electrophysiology.⁴⁷ Another review of 26 studies of the health impact of e-cigarette flavorants found detrimental effects of flavoring agents on the heart, lung, brain and other organs.⁴⁸ A 2024 paper showed that the flavoring agent ethyl vanillin used in e-cigarettes can induce energy pathway dysfunction and cellular stress responses in a renal model.

Vanillin and ethyl vanillin are among the most frequent flavor additives found in ENDS. These flavor chemicals impart a vanilla flavor and are components of dessert flavors that are especially popular among youth. In addition to imparting a sweet flavor, vanillin has also been shown in rodent studies to reward the circuitry triggering dopamine release in the brain and was

⁴² Erythropel HC, Jabba SV, DeWinter TM, et al. Formation of flavorant-propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids. *Nicotine Tob Res.* 2019;21(9):1248-1258. doi:10.1093/ntr/nty192

⁴³ Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. *Environ Sci Technol.* 2016;50(23):13080-13085. doi:10.1021/acs.est.6b05145

⁴⁴ Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, Jaspers I. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. *Am J Physiol Lung Cell Mol Physiol.* 2017 Aug 1;313(2):L278-L292. doi: 10.1152/ajplung.00452.2016. Epub 2017 May 11. PMID: 28495856; PMCID: PMC5582929

⁴⁵ Cox A, Brown KC, Bender C, Valentovic MA. The e-liquid flavoring cinnamaldehyde induces cellular stress responses in human proximal tubule (HK-2) kidney cells. *Biomed Pharmacother.* 2024 Jun;175:116666. doi:10.1016/j.biopha.2024.116666. Epub 2024 Apr 27. PMID: 38677246; PMCID:PMC11293278.

⁴⁶ Kuehl PJ, McDonald JD, Weber DT, Khlystov A, Nystoriak MA, Conklin DJ. Composition of aerosols from thermal degradation of flavors used in ENDS and tobacco products. *Inhal Toxicol.* 2022;34(11-12):319-328. doi:10.1080/08958378.2022.2103602. Epub 2022 Aug 1. PMID: 35913821; PMCID:PMC9830633.

⁴⁷ Abou-Assali O, Chidipi B, Chang M, Reiser M, Asswaytte R, Zhang Y, Long Duong VB, Szekeres C, Calcul L, Noujaim SF. Oxidative stress mediates cardiac electrophysiological injury in inhalation exposure to flavored vaping products. *Heart Rhythm.* 2026 Mar;23(3):751-765. doi: 10.1016/j.hrthm.2025.09.006. Epub 2025 Sep 8. PMID: 40930480.

⁴⁸ Sachdeva J, Karunanathan A, Shi J, Dai W, Kleinman MT, Herman D, Kloner RA. Flavoring Agents in E-cigarette Liquids: A Comprehensive Analysis of Multiple Health Risks. *Cureus.* 2023 Nov 18;15(11):e48995. doi: 10.7759/cureus.48995. PMID: 38111420; PMCID: PMC10726647.

shown to reinforce nicotine taking.^{49, 50, 51, 52, 53} Ethyl vanillin has been shown to slow nicotine metabolism, which extends its presence in the blood.⁵⁴

Vanillin and other flavor chemicals in e-cigarettes including uraneol, benzyl alcohol, ethyl maltol, ethyl vanillin, and corylone are significantly correlated with cytotoxicity. Pulegone and estragole levels are high enough in some e-cigarettes to present a risk for cancer.⁵⁵ A 2024 paper showed that the flavoring agent ethyl vanillin used in e-cigarettes can induce energy pathway dysfunction and cellular stress responses in a renal model.⁵⁶ Flavor agents such as delta-decalactone found in e-cigarettes may be linked to dysregulation of urinary biochemicals.⁵⁷

c. Synthetic cooling agents such as WS-3 and WS-23 should be added to the HPHC list

Mint, menthol, and other additives including synthetic cooling agents such as WS-3 and WS-23 reduce the harshness of nicotine products and improve taste.⁵⁸ This effect makes it easier for non-smokers, including youth, to initiate with products with high levels of nicotine, continue nicotine-product use, and to become addicted to nicotine products. Use of a cooling flavored

⁴⁹ Bagdas D, Zepei AM, Harris L, Minanov K, Jimenez JL, Addy NA. Impact of vanilla flavor on nicotine taste, choice, intake, and seeking behaviors. *Psychopharmacology (Berl)*. 2024;241(11):2241–53. Epub 20240606. doi: 10.1007/s00213-024-06630-9. PubMed PMID: 38839631; PMCID: PMC11836642.

⁵⁰ Swenson SM, Hill SP, Adeshina D, Hammers GV, McSweeney SM, Sword MK, Grooms MO, Maddox SK, Strcula HD, Olszewski NA, Tetteh-Quarshie S, Henderson BJ. Impact of chemical flavorants on reinforcement-related behavior in an adolescent mouse model of vaping self-administration. *J Pharmacol Exp Ther*. 2025;392(8):103651. Epub 20250701. doi: 10.1016/j.jpvet.2025.103651. PubMed PMID: 40706134.

⁵¹ Xu J, Xu H, Liu Y, He H, Li G. Vanillin-induced amelioration of depression-like behaviors in rats by modulating monoamine neurotransmitters in the brain. *Psychiatry Res*. 2015;225(3):509–14. Epub 20141209. doi: 10.1016/j.psychres.2014.11.056. PubMed PMID: 25595338.

⁵² Abuthawabeh R, Abuirmeileh AN, Alzoubi KH. The beneficial effect of vanillin on 6-hydroxydopamine rat model of Parkinson's disease. *Restor Neurol Neurosci*. 2020;38(5):369–73. doi: 10.3233/rnn-201028. PubMed PMID: 32986633.

⁵³ Du L, Xiao L, Zou C, Huang J. Vanillin attenuates the ethanol withdrawal syndrome and ethanol withdrawal induced anxiety by regulating the neurochemical balance. *Folia Neuropathol*. 2022;60(3):316–23. doi: 10.5114/fn.2022.118546. PubMed PMID: 36382484.

⁵⁴ Zhu Y, Wang H, Sun J, Liu F, Guo L, Zhang Q, Mao J, Tian S, Fan W, Xie J. Effects of flavor ingredient ethyl vanillin on nicotine pharmacokinetics and neurotransmitters release. *Eur J Pharmacol*. 2025;1002:177852. Epub 20250618. doi: 10.1016/j.ejphar.2025.177852. PubMed PMID: 40541599.

⁵⁵ Omaiye EE, Luo W, McWhirter KJ et al. Electronic cigarette refill fluids sold worldwide: flavor chemical composition, toxicity, and hazard analysis. *Chem Res Toxicol* 2020;33:2972–87.

⁵⁶ Cox AJ, Brown KC, Valentovic MA. The Flavoring Agent Ethyl Vanillin Induces Cellular Stress Responses in HK-2 Cells. *Toxics*. 2024;12(7):472. Published 2024 Jun 29.

⁵⁷ Hsiao Y-C, Matulewicz RS, Sherman SE et al. Untargeted metabolomics to characterize the urinary chemical landscape of E-cigarette users. *Chem Res Toxicol* 2023;36:630–42.

⁵⁸ Carstens E, Carstens MI. Sensory effects of nicotine and tobacco. *Nicotine Tob Res*. 2022;24(3):306–315. doi:10.1093/ntr/ntab086

ENDS at first use is associated with having a positive first vaping experience, which in turn was associated with greater likelihood of continued use.⁵⁹

Of particular concern, e-cigarette products labeled “unflavored” or “tobacco-flavored” frequently contain toxic flavor additives including menthol, synthetic cooling agents, and other flavorants. These so-called “tobacco-flavored” e-cigarette liquids are manipulated by manufacturers to have tastes that appeal to youth as well as adults. For example, damascenone is in many tobacco-flavored products together with pyrazines. Further, the term “tobacco-flavored” for e-cigarettes is misleading, since none contain extracts from tobacco. Rather, they are typically candy or vanilla flavored but renamed as “tobacco-flavored.” Several flavor chemicals, including ethyl maltol, vanillin, corylone, and other “confectionery-related” flavor chemicals, are abundant in some e-cigarette liquids (including for Puff Bar) labeled “tobacco-flavored,” coinciding with and apparently attempting to circumvent FDA’s restrictions on the sale of sweet and fruity-flavored e-cigarettes.⁶⁰

Particularly concerning is the fact that coolants are found in all e-cigarettes (not only those that are called “mint” or “menthol”) including “clear” (a concept flavor name that is often categorized as “unflavored”). Like mint and menthol, these cooling additives make nicotine more palatable and the products more appealing to youth. For example, in this 2025 study, the Flum Pebble Clear (“unflavored”) device had the highest total flavor chemical concentration of any product studied (96.4 mg mL⁻¹).⁶¹ Many e-cigarettes contain non-menthol synthetic cooling agents such as WS-3 and WS-23 and/or are labeled with ice-hybrid flavors such as “Raspberry Ice.”⁶² A 2025 study of “clear” e-cigarettes (introduced to evade Massachusetts flavor ban) shows that all “clear” e-liquids contain synthetic cooling agents WS-23 and/or WS-3, 18 of 19 studied products contained menthol, and 12 of 19 contained other flavorants and undermined the efficacy of the flavor ban.⁶³

A 2025 study of the cardiovascular health effects of flavorants and synthetic cooling agents such as WS-3 and WS-23 included in e-cigarettes labeled as “clear” found that the marketing of “clear” products with these additives resulted in health harms including a greater increase in blood pressure and heart rate.⁶⁴

⁵⁹ Barrington-Trimis JL, Stoolmiller M, Vogel EA, Harlow A, Tackett AP, Unger JB, McConnell R, Leventhal AM, Audrain-McGovern J, Sargent JD. Recall of Flavor at First E-cigarette Use and Its Association with E-cigarette Progression: The Mediating Effects of First Sensory Experience. *The Journal of pediatrics*. 2024 Dec 1;275:114246.

⁶⁰ Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. Ethyl maltol, vanillin, corylone and other conventional confectionery-related flavour chemicals dominate in some e-cigarette liquids labelled 'tobacco' flavoured. *Tob Control*. 2022;31(Suppl 3):s238-s244.

⁶¹ Robertson NE, Hunsaker HC, Yamamoto M, Cheung K, Poulin BA, Nguyen TB. E-liquid and aerosol characterization of popular disposable E-cigarettes. *ACS omega*. 2025 Jul 3;10(27):29615-27.

⁶² Leventhal AM, Tackett AP, Whitted L, Jordt SE, Jabba SV. Ice flavours and non-menthol synthetic cooling agents in e-cigarette products: a review. *Tob Control*. 2023 Nov;32(6):769-777. doi: 10.1136/tobaccocontrol-2021-057073. Epub 2022 Apr 28. PMID: 35483721; PMCID: PMC9613790.

⁶³ Minetti ET, Erythropel HC, Keith R, Davis DR, Zimmerman JB, Krishnan-Sarin S, Hamburg NM. Cardiovascular Health Effects and Synthetic Cooling Agents in E-Cigarettes Labeled as “Clear” Marketed in Massachusetts After the Tobacco Product Flavoring Ban. *Journal of the American Heart Association*. 2025 Aug 19;14(16):e036106.

⁶⁴ Minetti ET, Erythropel HC, Keith R, Davis DR, Zimmerman JB, Krishnan-Sarin S, Hamburg NM. Cardiovascular Health Effects and Synthetic Cooling Agents in E-Cigarettes Labeled as “Clear” Marketed in Massachusetts After the Tobacco Product Flavoring Ban. *Journal of the American Heart Association*. 2025 Aug 19;14(16):e036106.

Conclusion

1. We strongly support FDA's decision to add 18 new constituents to the list of Harmful and Potentially Harmful Constituents (HPHC), which reflect the more current range of tobacco and nicotine products under FDA's jurisdiction.
2. Flavor additives that are "Generally Recognized as Safe" (GRAS) when ingested as food does not mean they are safe when inhaled in tobacco and nicotine products. Therefore, FDA must recognize and act on the fact that many flavor additives in food that have obtained GRAS designation are harmful when added to inhalable products and should be added to the HPHC list.
3. We strongly support FDA's proposal to add pulegone, furfuryl alcohol, and methyl eugenol to the HPHC list. These constituents are frequently added to e-liquid formulations and flavors and are associated with significant health harms.
4. We recommend that FDA add cinnamaldehyde, vanillin, ethyl vanillin, and cooling agents such as WS-3 and WS-23 to the HPHC list based on significant scientific evidence demonstrating their health harms.