

**CTP should finalize its updated list of Harmful and Potentially Harmful Constituents
by December 2023**

**Docket No. FDA–2023–N–2873
Developing FDA’s Center for Tobacco Products’ Strategic Plan**

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FDA announced¹ a Public Meeting and Listening Session and an opportunity to submit written public comments to obtain feedback on five proposed strategic goals it is using to develop a strategic plan for FDA’s Center for Tobacco Products’ (CTP) comprehensive Strategic Plan. In particular, CTP asked for specific actions it could take in the next 5 years that would have significant impact on reducing tobacco-related death and disease. ***One of these specific actions should be to immediately complete the process of updating the outdated Harmful and Potentially Harmful Constituents (HPHC) list and commit to revisiting it every three years to ensure that it reflects important potential toxicants in evolving tobacco products and new evidence.***

This principle particularly applies to strategic goals 1 and 2:

1. Develop, Advance, and Communicate Comprehensive and Impactful Tobacco Regulations and Guidance.

2. Ensure Timely, Clear, and Consistent Product Application Review to Protect Public Health.

¹ US Food and Drug Administration, CTP Newsroom, Listening Session: Developing FDA’s Center for Tobacco Products’ Strategic Plan, August 22, 2023 (July 21, 2023). Available: https://www.fda.gov/tobacco-products/ctp-newsroom/listening-session-developing-fdas-center-tobacco-products-strategic-plan-08222023?utm_campaign=ctp-ruf&utm_content=landingpage&utm_medium=email&utm_source=govdelivery&utm_term=stratcomms#Proposed%20Strategic%20Goals

- In April 2012, FDA issued a list of Harmful and Potentially Harmful Constituents (HPHCs)² in Tobacco Products and Tobacco Smoke that included 93 HPHCs.
- This list, which is dominated by carcinogens and other toxicants in cigarette smoke, has become the *de facto* metric for judging the harm of tobacco products.
- The list created in 2012 does not reflect the current range of tobacco products now subject to CTP’s tobacco product authorities including electronic cigarettes and heated tobacco products that deliver toxicants not observed in or at higher levels than in cigarette smoke.
- Use of the 2012 list to judge new products may, therefore, underestimate health effects of new products.
- Recognizing that the list needed to be updated, in August 2019, FDA sought public comment^{3, 4} on its proposal to add 19 particular toxicants, which included constituents in e-cigarettes and e-liquids, to the outdated 2012 list of HPHCs.
- The 19 toxicants FDA proposed to add to the HPHC list are: acetic acid, acetoin, (also known as 3-hydroxy-2-butanone), acetyl propionyl (also known as 2,3-pentanedione), benzyl acetate, butyraldehyde, diacetyl, diethylene glycol, ethyl acetate, ethyl acetoacetate, ethylene glycol, furfural, glycerol, glycidol, isoamyl acetate, isobutyl acetate, methyl acetate, n-butanol, propionic acid, propylene glycol.
- The public comment period closed on October 4, 2019, and only 40 comments in total were submitted (Table 1).
 - 14 endorsed the proposed HPHC update
 - i. 6 suggested additional toxicants (48 pages)
 - ii. 8 endorsed the list without suggesting additions (11 pages)
 - 6 opposed at least some additions (50 pages)
 - 3 submitted information without making specific suggestions about list items (15 pages)
 - 14 did not make specific suggestions about the list (11 pages)
 - 3 were duplicates or endorsements of other comments
- All of these public comments are incorporated by reference.
- In addition to the 19 additional constituents proposed by FDA, the 6 public comments that urged FDA to add compounds that may cause pulmonary or cardiovascular harms or be carcinogenic when inhaled, especially oils and chemicals and chemical classes found in e-cigarette flavorants, with several commenters suggesting the same additions:
 - UCSF TCORS: pulegone, vitamin E acetate, acetoin, maltol, ortho-vanillin (or “o-vanillin”), coumarin, cinnamaldehyde, menthol, α,β -unsaturated carbonyl compounds, 1,2-dicarbonyl compounds, furans, epoxides

² FDA, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List (April 2012). Available at: <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list>

³ <https://www.fda.gov/news-events/fda-brief/fda-brief-fda-seeks-comment-proposed-additions-list-harmful-and-potentially-harmful-constituents>

⁴ FDA, Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments, August 5, 2019, 84 FR 38032. Available: <https://www.federalregister.gov/documents/2019/08/05/2019-16658/harmful-and-potentially-harmful-constituents-in-tobacco-products-established-list-proposed-additions>

- AHA Tobacco Regulation and Addiction Center: cinnamaldehyde, menthol, eugenol, citronellol, limonene, vanillin, dimethylpyrazine, eucalyptol, acetylpyridine, and sucralose.
- American Thoracic Society: chocolate flavor (2,5-dimethylpyrazine), 2,3-hexanedione, benzaldehyde, cinnamaldehyde, maltol, mint/menthol, vanillin
- Ohio State University: furfuryl alcohol, 5-(hydroxymethyl)-2-furaldehyde
- Schlesinger Law Group: benzo[e]pyrene, N'-nitrosoanabasine, dioxins and di-benzofurans, 2- and 3-Methylfuran, total particulate matter
- Respira Technologies: hexavalent chromium
- There were several suggestions for using additional criteria for additions to the HPHC list, including:
 - UCSF TCORS suggested that FDA should use as additional criteria for additions to the HPHC list, including constituents identified by California's Proposition 65 list of carcinogens and reproductive toxicants and the California Air Resources Board's list of Toxicant Air Contaminants.
 - AHA Tobacco Regulation and Addiction Center suggested that the FDA should incorporate evidence for cardiac QT-prolonging effects of constituents into their criteria for HPHCs. As well, the potential of e-liquid constituents to generate HPHCs upon heating and aerosolization in ENDS should be added as criteria for HPHCs.
- The 6 critical comments (from industry) often made similar points and were specific enough that FDA can easily respond, including with reference to additional material in the supportive comments.
- The small volume of comments, their brevity and focus, and common themes means that incorporating the information in these public comments is not a major task.
- As a recent paper by Tehrani et al⁵ explains, there are thousands of unknown chemicals in e-liquids, and the number of compounds increase significantly in the aerosol. These potential toxicants include hydrocarbon-like compounds that are typically associated with combustion, but which manufacturers say are not produced during vaping. The main take-away from this study is that a large number of different and unknown compounds are present in e-liquids and are formed during the vaping process that may not be present in cigarettes. While e-cigarettes may not contain the same toxicants found in cigarettes, their potential risks must be recognized and studied. The existing list of HPHCs focuses on toxicants found in cigarettes. The proposed expansion, with the suggested additions, will be an important step toward expanding the HPHC list to include the huge number of compounds found in e-cigarettes that are potential toxicants.
- One of the comments submitted by the Flavor and Extract Manufacturers Association (FEMA)⁶ emphasized the fact that the FEMA Expert Panel 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

⁵ Tehrani MW, Newmeyer MN, Rule AM, Prasse C. Characterizing the Chemical Landscape in Commercial E-Cigarette Liquids and Aerosols by Liquid Chromatography-High-Resolution Mass Spectrometry. *Chem Res Toxicol.* 2021 Oct 5. doi: 10.1021/acs.chemrestox.1c00253. Epub ahead of print. PMID: 34610237.

⁶ <https://www.regulations.gov/comment/FDA-2012-N-0143-0055>

in the U.S.” Further, FEMA referred to its “long-standing statement⁷ 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.”⁸

In summary, the FDA should immediately act to update the HPHC list, including the additional toxicants recommended in the 2019 public comment period:

- FDA should finalize the updated the HPHC list by December 2023 and begin using the new list to guide product assessments to protect the public health.
- Given its centrality to decision making in the face of a rapidly evolving tobacco product market as well as evidence on toxicants, the FDA CTP Strategic Plan should include regularly reviewing and updating the HPHC list at least every 3 years.

⁷ <https://www.femaflavor.org/sites/default/files/2018-05/FEMAGRAS%20Ecig%2004302018.pdf>

⁸ <https://www.regulations.gov/comment/FDA-2012-N-0143-0055>

Table 1: Summary of public comments submitted regarding updated HPHC list			
Number*	Commenter	Comment	Pages
Supportive of updated HPHC list: Also Recommend additional toxicants			
0037	UCSF TCORS (submitted by Lauren Lempert)	Supports additions; proposes additional additions	18 23-page appendix
0057	AHA Tobacco Regulation and Addiction Center (submitted by Anonymous)	Supports additions to HPHL list; suggests additional criteria for adding to list and compounds to be added	11
0041	American Thoracic Society	Notes that GRAS applies to ingested not inhaled compounds; proposes several additional additions to list	6
0046	Ohio State University	Supports additions to list; suggests other additions	6
0040	Schlesinger Law Offices	Supports additions to list; suggests other additions	3
0047	Mario Danek (Respira Technologies)	Supports expanded list; proposes additional additions; need to consider breakdown products in ENDS aerosol	4
Supportive of updated HPHC list: No suggested additions			
0042	American Academy of Pediatrics, American Cancer Society Cancer Action Network, American Heart Association, Campaign for Tobacco-Free Kids, Truth Initiative	Supports proposed additions to HPHC list	2
0053	Al Fakher Tobacco Factory FZE	Supports additions to HPHC list; raises questions about testing requirements	3
0045	Elizabeth Camp	Support for additions to HPHC list	1
0021	Edgardo	Supports proposed additions to HPHC list	1
0028	Gregory Robarti	Supports adding PG to HPHC list	1
0038	Adrian Torres	Supports proposed additions to HPHC list	1
0024	Mary Townsend	Support for adding Diacetyl and 2,3-Pentanedione	1
0035	Preston Campbell	Suggests adding compounds in e-cigarette aerosol	1
Opposes at least some additions to HPHC list			
0059	Altria	Some additions outside scope, need for established lab tests, support for harm reduction and continuum of risk	11
0039	Philip Morris Products SA	Supports updating list; critical of some specific additions as not meeting FDA criteria for being "toxicants"	14
0043	RAI Services Company	Opposes expanded list on grounds that the additions do not meet FDA's stated criteria; critical of NIOSH	22
0020	Richard Riva	Clarify which labs to use and test protocols for HPHC testing	1
0044	Jonathan Golden	Nothing should be added to HPHC list	1
0027	Nathan Affield	Opposes adding PG because it is GRAS as a food ingredient	1
Submitted information without making specific recommendation about what is on the HPHC list			
0055	Flavor and Extract Manufacturers Association	GRAS does not apply to inhaled substances	3
0048	American Chemistry Council	Overview of recent research on ethylene glycol and diethylene glycol; no specific recommendation	6

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0058	American Chemistry Council	Summarizes several PG studies; no specific recommendation	6
Comments that did not make specific suggestions about what is on the HPHC list			
0054	Cigar Rights Association of America and Premium Cigar Association	Requests delay in reporting HPHCs for cigars, requests premium cigars be exempt from HPHC testing	20
0029	Cathleen Reese	Chemicals in secondhand tobacco smoke linked to breast cancer; no specific suggestions regarding HPHC list	1 10 attached papers
0030	Fran Forbes	Value of vaping and flavors for smoking cessation	1
0031	Amber Cooper	Value of vaping for smoking cessation	1
0032	Paul Hartig	Ban e-cigarette TV ads	1
0033	Betty Faust	Criticizes FDA inaction on JUUL; nothing about HPHC list	1
0034	Emily Austin	Supports e-cigarettes for cessation	1
0036	Janis Jeffreys	Value of vaping for smoking cessation	1
0049	Duke University	No comment attached	0
0050	Duke University	No comment attached	0
0051	Duke University, Yale University	No comment attached	0
0022	George Harakas	Opposes "bad science"	1
0023	Mike Grim	Recommends disclose ingredients	1
0025	Dwain Sparks	Add CAS number for compounds on HPHC list	1
Duplicates or simply endorses another comment			
0026	Mary Townsend	Support for adding Diacetyl and 2,3-Pentanedione (duplicate of 0024)	1
0056	Cigar Rights Association of America and Premium Cigar Association	Requests delay in reporting HPHCs for cigars, requests premium cigars be exempt from HPHC testing (duplicate of 0054)	20
0052	Oliva Cigar Company	Supports comment submitted by Cigar Rights of America (comments 0054 and 0056)	1
* https://www.regulations.gov/docket/FDA-2012-N-0143/comments			