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June 10, 2015

Dr. Dennis Keefe
Director of the Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD 20740

Re: Food additive petition pursuant to 21 USC § 348 seeking amended food additive regulation to: 1) remove FDA's approval at 21 CFR § 172.515 of seven synthetic flavors; and 2) add to that section a prohibition on use of these seven flavors and one additional flavor approved as GRAS by the flavor industry because all eight have been found by the National Toxicology Program to induce cancer in man or animal.

Dear Dr. Keefe:

Since 1958, federal law has stated that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . ." (21 U.S.C. § 348(c)(3)(A)). This requirement, known as the Delaney Clause in honor of its Congressional author, is a bright line drawn by Congress on what is not safe in food with respect to carcinogens. This statutory requirement for food additives has not been altered in the intervening half-century.

We hereby submit this food additive petition to the Food and Drug Administration (FDA), pursuant to 21 USC § 348, to remove its approval of seven synthetic flavors or adjuvants from 21 CFR § 172.515 because they are not safe for use in food pursuant to the Delaney Clause. Each has been found by the Department of Health and Human Services' (HHS) National Toxicology Program (NTP) to induce cancer in man or animal using tests done consistent with FDA's guidance[1] for toxicology studies for food ingredients.[2]

We also petition FDA to explicitly establish a zero tolerance in 21 CFR § 172.515 for the use of these seven flavors as well as one flavor, *trans,trans*-2,4-hexadienal, approved by the Flavor and Extract Manufacturers Association's (FEMA) expert panel as "generally recognized as safe"

[1] FDA, Guidance for Industry and Other Stakeholders: Toxicology Principles for the Safety Assessment of Food Ingredients (Redbook 2000), 2007. Chapter IV.C.6. Accessed May 23, 2015. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.
[2] See Appendix 1 and 3 for details.

(GRAS). NTP has found that this FEMA GRAS flavor induces cancer in man or animal.[3] The eight synthetic flavors are:

1. **Benzophenone** (also known as diphenylketone);
2. **Ethyl acrylate;**
3. **Eugenyl methyl ether** (also known as 4-allylveratrole or **methyl eugenol**);
4. **Myrcene** (also known as 7-methyl-3-methylene-1,6-octadiene);
5. **Pulegone** (also known as *p*-menth-4(8)-en-3-one);
6. **Pyridine**;
7. **Styrene**; and
8. ***Trans,trans*-2,4-hexadienal**.

For chemicals whose addition to food would violate the Delaney Clause, a zero tolerance is the only appropriate condition of use consistent with 21 U.S.C. § 348. The explicit prohibition is essential because their use has been allowed by FEMA[4] for more than 40 years in food and clarity is necessary to prevent their continued use. Mere revocation of approved food additive status would be insufficient under current law and rules to assure that companies would stop using them pursuant to a private GRAS determination regarding a particular condition of use. For reasons elaborated upon below, a GRAS determination for carcinogens would be manifestly an abuse of the statute. Nonetheless, it occurs as a matter of regulatory practice, as the FEMA designations demonstrate. It is, therefore, appropriate – and even necessary – to use the food additive petition process to set a zero tolerance for substances deemed carcinogenic to prevent any trade association or individual food manufacturers from continuing to claim they are safe.[5]

We also ask that FDA remove these eight synthetic flavors from its "Everything Added to Food in the United States" (EAFUS) database. We also ask FDA to remove two additional carcinogenic flavors, **acetamide**[6] and **quinoloine,**[7] from EAFUS. FEMA determined that these

[3] See Appendix 1 and 3 for details.
[4] As noted in Appendix 1 and 3, shortly after FDA approved the seven synthetic flavors as food additives, FEMA designated them as GRAS and set numerical limits for their use in food and beverage.
[5] Nothing in the statute or regulations limits the use of a food additive petition to prohibit a substance's specific uses in food. The statute at 21 U.S.C. § 348(a) states that "A food additive shall, with respect to any particular use or in intended use of such additives, be deemed unsafe for the purposes of the application of clause (2)(C) of section 402(a) . . . ." In addition, 21 CFR § 170.38(c) refers to "discontinuation of the use of the additive" as an option when FDA determines that a substance is a food additive. It would be illogical for FDA to assert that a food additive petition is permissible to restrict the use of a substance in food but is not allowed to establish a zero tolerance for the same substance simply because the agency has chosen for administrative convenience to prohibit some food additives in a different part of its regulations than those used for most food additives. FDA's decision to identify substances prohibited from use in human food at 21 CFR Part 189 as something other than food additives was for its administrative convenience in the same way FDA lists prohibited substances in its Everything Added to Food in the United States (EAFUS) database.
[6] IARC, Acetamide, IARC Monograph – Volume 71-59, 1999, pp. 1211-1221. See http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-59.pdf.
[7] OEHHA, Evidence on the Carcinogenicity of Quinoline and its Strong Acid Salts, 1997. See www.oehha.ca.gov/prop65/hazard_ident/pdf_zip/quinolin.pdf.

two flavors are no longer GRAS in 2009[8] and 2014[9] respectively, but FDA still lists them in EAFUS.[10] FDA should remove them from EAFUS because food manufacturers may mistakenly rely on FDA's inaccurate database.

FDA approved the seven food additives in 1964 and set no numerical limit on how much may be used in food.[11] The only limit is Good Manufacturing Practices at 21 CFR § 172.515(a), meaning the additives are used in the minimum quantity required to produce their intended flavoring effect and otherwise in accordance with all the principles of good manufacturing practice. Shortly after FDA's approval, FEMA designated the same flavors as GRAS, giving them a FEMA number and describing average maximum use level in various foods considered by the trade association to be safe. In 1974, FEMA designated *trans,trans*-2,4-hexadienal as a GRAS flavor and reaffirmed it as safe in 2003 despite NTP finding that the chemical induced cancer in animals. See Appendix 1 and 3.

After FDA and/or FEMA determined that these eight synthetic flavor additives were safe, NTP found that each induced cancer in man or animal when ingested.[12] NTP's findings were based on ingestion studies done consistent with FDA's Redbook.[13] NTP made these findings pursuant to a Congressional directive at 42 U.S.C. § 241 to the HHS Secretary to conduct these types of tests. The Secretary established NTP to perform this work.

Congress also mandated at 42 U.S.C. § 241(b)(4) that the Secretary publish a biennial report listing substances: 1) which are known to be carcinogens or may reasonably be anticipated to be carcinogens, and 2) to which a significant number of persons residing in the United States are exposed. With the Secretary's approval, NTP has designated two of these eight synthetic flavors additives, **methyl eugenol and styrene**, as "reasonably anticipated to be a human carcinogen" in its biennial report known as the Report on Carcinogens.[14]

Other recognized authorities, such as the International Agency for Research on Cancer (IARC) and California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA), also evaluated some of the eight synthetic flavors and like NTP found evidence to conclude that the flavors should be considered to induce cancer in man or animal.

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[8] FEMA delisted acetamide at FEMA Expert Panel (R.L. Smith, W.J. Waddell, S.M. Cohen, V.J. Feron, L.J. Marnett, P.S. Portoghese, I.M.C.M. Rietjens, T.B. Adams, C. Lucas Gavin, M.M. McGowen, S.V. Taylor, and M.C. Williams), GRAS Flavoring Substances 24 (FEMA No. 4430-4666), *Food Technology*, Vol. 06-09 (2009).
[9] FEMA delisted quinoline in its FEMA Expert Panel, Interim GRAS Flavoring Substances 27, 2014 accessed at http://www.femaflavor.org/sites/default/files/Interim%20GRAS%2027%20Nov_2014.pdf.
[10] FDA, Everything Added to Food in the United States, accessed May 23, 2014, http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=eafusListing.
[11] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).
[12] See Appendix 1 and 3 for details.
[13] FDA, Guidance for Industry and Other Stakeholders: Toxicology Principles for the Safety Assessment of Food Ingredients (Redbook 2000), 2007. Chapter IV.C.6. Accessed May 23, 2015. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.
[14] NTP, Report on Carcinogens, Thirteenth Edition, 2014. See http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.

- IARC designated six of the eight substances as Group 2B carcinogens[15] based primarily on the finding that they induce cancer in animals (see Appendix 1 and 3) and is evaluating a seventh (beta-myrcene).[16] IARC is the science program of the World Health Organization (WHO) that was launched in 1965 to provide critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures and publishes its designations in Monographs on the Evaluation of Carcinogenic Risks to Humans.[17] The U.S. President's Cancer Panel described IARC's monographs on carcinogenesis as "the 'gold standard' in evaluating evidence on cancer-causation . . ."[18]
- OEHHA designated seven of the eight flavors as carcinogens (see Appendix 1 and 3) and required warning to consumers as part of the Safe Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65).[19] In 2015, OEHHA proposed listing the eighth flavor (styrene) as a carcinogen.[20]

Based on the above conclusions by recognized authorities responsible for determining whether a substance is found to induce cancer when ingested by man or animal, FDA should remove its approval for these seven additives and prescribe a zero tolerance for them, as well the eighth flavor designated only by FEMA as GRAS.

We note that, under the law, there is no reason for FDA to conduct its own hazard analysis of the carcinogenicity of these substances given this clear body of evidence, including conclusions from NTP, FDA's sister program within HHS. FDA's analysis should be limited to determining whether the NTP study protocols were "tests appropriate for the evaluation of the safety of food additives" under the Delaney Clause. (21 U.S.C. § 348(c)(3)(A)) Since they are consistent with the Redbook, we maintain that this evaluation could be done quickly. Therefore, a *de novo* investigation is unnecessary and could delay the agency taking action within the 90-day statutory deadline. If FDA decides to conduct its own hazard analysis or determines that the NTP study protocols are inappropriate, we request notification in writing from the agency. Such notice should be made no later than in the letter sent 90 days after the agency files the petition.

Our reliance on respected recognized authorities has precedent within FDA. With the unanimous support of FDA's Tobacco Products Scientific Advisory Committee, the agency's Center for Tobacco Products classifies chemicals as Hazardous / Potentially Hazardous Constituents (HPHC) using similar criteria. For instance, the committee recommended chemicals be considered carcinogens if they are listed as:

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[15] See Appendix 1 and 3 for details.
[16] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, INTERNAL REPORT 14/002, Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015–2019, 2014. http://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf.
[17] IARC, Preamble to the Monographs, accessed on May 23, 2015 at http://monographs.iarc.fr/ENG/Preamble/currenta1background0706.php
[18] The President's Cancer Panel, Reducing Environmental Cancer Risk: What We Can Do Now, 2008-2009 Annual Report of the President's Cancer Panel, 2010. See http://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf.
[19] OEHHA, Proposition 65, accessed on May 23, 2015 at http://www.oehha.ca.gov/prop65.html.
[20] OEHHA, Proposition 65, Notice of Intent to List: Styrene, 2015. See http://www.oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilstyrene2015.html.

- IARC Group 1 (carcinogenic to humans) or 2A (probably carcinogen to humans) or 2B (possibly carcinogenic to humans);
- Environmental Protection Agency (EPA) known, likely, probable, or possible human carcinogen; or
- NTP human carcinogen or reasonably anticipated to be a human carcinogen.[21]

FDA also relies on these authorities with respect to food additives. For example, FDA's Office of Food Additive Safety relied on an NTP toxicology and carcinogenesis study on *ginkgo biloba* leaf extract in a warning letter issued to a food manufacturer finding that the extract was an unapproved food additive.[22]

We understand from FDA that some in the agency and in industry maintain that the Delaney Clause does not apply to GRAS substances. These individuals claim that if a chemical is found to induce cancer when ingested by man or animal, it may be intentionally added to food as GRAS even if it could never be approved as a food additive. This position is untenable under the law. Were it to apply, a food additive that would be disallowed under Delaney would be permissible as long as the manufacturer secretly or publically characterized the substance as "GRAS," whether generally or for that condition of use. Thus, GRAS would be an easy route for carcinogenic substances to avoid the explicit ban on carcinogenic food additives established by Congress. Yet as the design of the statute makes clear, Congress would never have intended to hold GRAS substances, as the target of less regulation and the subject of a requirement for general knowledge of safety, to a less onerous safety standard than food additives.

Rather, as the legislative history amply demonstrates,[23] Congress intended most new and potentially dangerous substances to receive more exacting review by FDA under the food additive petition process. Carcinogenic substances, as specifically highlighted by the Delaney Clause, certainly belong in such a category. Thus, any likely carcinogens must necessarily be assessed as food additives, subject to the Delaney Clause, even if they were once considered GRAS.[24]

Our view is consistent with FDA's own regulations. FDA regulations expressly state that the same safety standard applies to food additives and GRAS substances. Under the current

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[21] FDA, Tobacco Products Scientific Advisory Committee, Summary of minutes of August 30, 2010. See http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM233611.pdf. See also FDA, Criteria developed for identifying an initial list of harmful and potentially harmful (H/PH) constituents in tobacco products or tobacco smoke and Summary of major recommendations of the Constituent subcommittee. See http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm180903.htm.

[22] FDA, Warning Letter SEA 13-15 to Stewart Brothers, 2013, http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2013/ucm346316.htm.

[23] For an in-depth discussion of the legislative history of the Food Additive Amendment of 1958, see Comment by Center for Science in the Public Interest (CSPI), Consumers Union, Environmental Working Group (EWG), and Natural Resources Defense Council (NRDC) re: Substances Generally Recognized as Safe, available at http://cspinet.org/new/pdf/GRAS%20Comment%20FINAL.pdf.

[24] Moreover, if Delaney did not apply to GRAS, any independent GRAS determinations by manufacturers of likely carcinogens would be plainly insufficient to support a "general recognition of safety," as neither FDA nor the food industry currently collects or reports on the cumulative effects information necessary to address the safety of any condition of use.

regulations, GRAS status based on scientific procedures "require[s] the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient."[25] FDA has further clarified that a GRAS substance is "neither more safe nor less safe than approved food additives."[26] Instead, a GRAS substance is distinguished from a food additive only on the basis of the degree of *common knowledge* about the safety of the substance.[27] This means that, applying FDA's own regulations, the Delaney Clause *must* apply to GRAS substances, because such substances cannot be less safe than food additives.

With this food additive petition, we ask that FDA amend 21 CFR § 172.515 to explicitly prohibit the use of these eight carcinogens in food.

Appendix 1 contains the list of the eight synthetic flavor additives providing: 1) the additive name; 2) the Chemical Abstract Service (CAS) No.; 3) FEMA No. and year of evaluation by the FEMA Expert Panel; 4) uses and average maximum use level considered by FEMA to be safe; and 5) authority designating the flavor as a carcinogen and year of designation sorted with most recent first.

Appendix 2 provides additional details on the petition required by 21 CFR Part 172; Appendix 3 supplies relevant reports on the carcinogenicity of the flavors; and Appendix 4 presents the specific changes we seek in the regulation. This letter, all appendices, and materials provided on a CD-ROM constitute our complete food additive petition.[28] We have enclosed three copies per 21 CFR § 171.1. This petition contains no confidential information, so we ask that FDA include it in the docket for any regulatory action it takes so the public can assess the information.

If FDA grants this petition, it will have a positive impact on the environment and public health by reducing exposure to these eight non-essential substances. No flavor or flavor extract is essential. With more than 2000 additional flavor additives allowed in food, the industry can either eliminate the flavor without substitution or find a safer alternative.

If you have questions or comments, please contact Tom Neltner, our agent on this petition, at tneltner@gmail.com or 317-442-3973, and copy Erik D. Olson at eolson@nrdc.org, Dr. Maricel Maffini at drmvma@gmail.com, and Laura MacCleery at lmaccleery@cspi.org on all responses.

Sincerely,

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[25] 21 C.F.R. § 170.30(b). See also FDA, Guidance for Industry: Frequently Asked Questions About GRAS, 2004. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm061846.htm.

[26] Substances Generally Recognized as Safe, 62 Fed. Reg. 18938, 18942 (Apr. 17, 1997).

[27] *Id.* at 18940.

[28] Please note that this is NOT a citizen petition.

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Appendix 1: Flavors found by NTP to induce cancer in man or animal and designated as a carcinogen by a recognized authority

Table 1: Flavors designated as a carcinogen by a recognized authority and found by NTP to induce cancer in man or animal

Additive name	CAS No.	FEMA No. & Year (GRAS Report No.)	Flavor uses and FEMA's average maximum use level considered GRAS in parenthesis	Authority and designation year (sorted with most recent first)
Benzophenone / Diphenylketone	119-61-9	2134 in 1965 (GRAS 3)[a]	Baked goods (2.4 ppm); ice cream, ices etc. (0.61 ppm); beverages (0.5 ppm); and candy (1.7 ppm)	Calif. Prop. 65 Carcinogen (2012)[i] / NTP Study (2006)[j] concluded it caused cancer in two species / IARC Possibly Carcinogenic to Humans (2B) (1999)[k]
Ethyl acrylate	140-88-5	2418 in 1965 (GRAS 3)[a]	Candy and baked goods (1.1 ppm); beverages (0.13-0.26 ppm); ice cream, ices etc. (0.06-1 ppm); and chewing gum (0.1 ppm)	IARC Possibly Carcinogenic to Humans (2B) (1999)[l] / Calif. Prop. 65 Carcinogen (1989)[m] / NTP Study (1986)[n] concluded it was carcinogenic in two species.
Eugenyl methyl ether / 4-Allylveratrole / Methyl eugenol.	93-15-2	2475 in 1965 (GRAS 3)[a] / Reaffirmed in 2001 (GRAS 20)[b] / Reaffirmed in 2002[c]	Jellies (52 ppm); baked goods (13 ppm); candy (11 ppm); beverages (10 ppm); and ice cream, ices etc. (4.8 ppm)	IARC Possibly Carcinogenic to Humans (2B) (2004)[o] / NTP Reasonably Anticipated To Be Human Carcinogen (2002)[p, q] / Calif. Prop. 65 Carcinogen (2001)[r] / NTP Study (2000)[s] found clear evidence of carcinogenic activity in two species.
Myrcene / 7-methyl-3-methylene-1,6-octadiene	123-35-3	2762 in 1965 (GRAS 3)[a]	Candy (0.50-13 ppm); ice cream, ices etc. (6.4 ppm); baked goods (4.9 ppm); and beverages (4.4 ppm)	Calif. Prop. 65 Carcinogen (2015)[t] / NTP Study (2010)[u] concluded it caused cancer in two species.
Pulegone / p-Menth-4(8)-en-3-one.	89-82-7	2963 in 1965 (GRAS 3)[a] Reaffirmed in 2005 (GRAS 22)[d]	Baked goods (24-25 ppm); candy (17 ppm); ice cream, ices etc. (5-32 ppm); and beverages (5-8 ppm)	Calif. Prop. 65 Carcinogen (2014)[v] / IARC Possibly Carcinogenic to Humans (2B) (2014)[w] / NTP Study (2011)[x] found clear evidence of carcinogenic activity in two species.
Pyridine	110-86-1	2966 in 1965 (GRAS 3)[a] Reaffirmed in 2011 (GRAS 25)[e]	Beverages (1 ppm); candy and baked goods (0.4 ppm); and ice cream, ices etc. (0.02-0.12 ppm);	Calif. Prop. 65 Carcinogen (2002)[y] / NTP Study (2000)[z] found clear evidence of carcinogenicity in one species.
Styrene	100-42-5	3233 in 1967 (GRAS 4)[f]	Ice cream, ices etc., candy and baked goods (0.2 ppm)	NTP Reasonably Anticipated To Be Human Carcinogen (2011)[aa, bb] / IARC Possibly Carcinogenic to Humans (2B) (2002)[cc]
Trans,*trans*-2,4-hexadienal	142-83-6	3429 in 1974 (GRAS 8)[g] Reaffirmed in 2003 (GRAS 21)[h]	Frozen desserts, confectionary, puddings, gelatins, jams, condiments, and pickles (4 ppm); beverages (4 ppm / 1 ppm if alcoholic); and preserves and spreads (2 ppm)	IARC Possibly Carcinogenic to Humans (2B) (2012)[dd] / Calif. Prop 65 Carcinogen (2005)[ee] / NTP Study (2003)[ff] found clear evidence of carcinogenic activity in two species.

Table 1: Flavors designated as a carcinogen by a recognized authority and found by NTP to induce cancer in man or animal

Additive name	CAS No.	FEMA No. & Year (GRAS Report No.)	Flavor uses and FEMA's average maximum use level considered GRAS in parenthesis	Authority and designation year (sorted with most recent first)

CAS = Chemical Abstract Service
FEMA = Flavor and Extract Manufacturers Association
GRAS = Generally Recognized as Safe
IARC = International Agency for Research on Cancer (part of World Health Organization)
NTP = National Toxicology Program

See next page for references.

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t. OEHHA, Chemical Listed Effective March 27, 2015 as Known to the State of California to Cause Cancer: Beta-Myrcene, 2015. http://oehha.ca.gov/prop65/CRNR_notices/list_changes/032415listbetamyrcene.html.
u. NTP, Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2010. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr557/index.html.
v. OEHHA, Chemicals Listed Effective April 18, 2014 as Known to the State of California to Cause Cancer: Pentosan Polysulfate Sodium, Pioglitazone, Trimteerene, and Pulegone, 2014. http://oehha.ca.gov/prop65/prop65_list/041814P65list.html.
w. IARC, Pulegone, IARC Monograph – Volume 108-05, 2014, pp. 1-14. See http://monographs.iarc.fr/ENG/Monographs/vol108/mono108-05.pdf.
x. NTP, Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2011. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr563/index.html.
y. OEHHA, Chemical Listed Effective May 17, 2002 as Known to the State of California to Cause Cancer: Pyridine, May 17, 2002. See http://oehha.ca.gov/prop65/out_of_date/51702notice.html.
z. NTP, Toxicology and Carcinogenesis Studies of Pyridine (CAS No. 110-86-1) in F344/N Rats, Wistar Rats, and B6C3F$_1$ Mice (Drinking Water Studies), 2000. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr400499/abstracts/tr470/index.html.
aa. NTP, Report on Carcinogens, Thirteenth Edition, Styrene, 2014. See http://ntp.niehs.nih.gov/go/roc13.
bb. NTP, Final Report on Carcinogens Background Document for Styrene, 2008. See http://ntp.niehs.nih.gov/pubhealth/roc/listings/s/styrene/summary/index.html.
cc. IARC, Styrene, IARC Monograph – Volume 82-9, 2002, pp. 437-550. See http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf.
dd. IARC, 2,4-Hexadienal, IARC Monograph – Volume 101-012, 2012, pp. 391-405. See http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-012.pdf.

ee. OEHHA, Chemical Meeting the Criteria for Listing as Causing Cancer Via the Authoritative Bodies Mechanism, Package 23, 2004. See http://www.oehha.ca.gov/prop65/CRNR_notices/state_listing/data_callin/pdf/ABpkg23.pdf.
ff. NTP, Technical Report on the Toxicology and Carcinogenesis Studies of 2,4-Hexadienal (89% *trans,trans* isomer, CAS No. 142-83-6; 11% *cis,trans* isomer) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2003. See http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr509.pdf.

Appendix 2
Responses to elements required by 21 CFR § 171.1

Per 21 CFR § 171.1, we provide responses to the requested elements of a food additive petition with one element per page.

Name and Pertinent Information Concerning Food Additive
The identity of the food additives are as follows:

Additive name	Chemical formula	Formula weight	FEMA No.	CAS No.	INS No.	UNI No
Benzophenone / Diphenylketone	C13H10O	182	2134	119-61-9	*	*
Ethyl acrylate	C5H8O2	100	2418	140-88-5	*	*
Eugenyl methyl ether / 4-Allylveratrole / Methyl eugenol.	C11H14O2	178	2475	93-15-2	*	*
Myrcene / 7-methyl-3-methylene-1,6-octadiene	C10H16	136	2762	123-35-3	*	*
Pulegone / *p*- Menth-4(8)-en-3-one.	C10H16O	152	2963	89-82-7	*	*
Pyridine	C3H6O	58	2966	110-86-1	*	*
Styrene	C8H8	104	3233	100-42-5	*	*
Trans,trans-2,4-hexadienal	C6H8O	96	3429	142-83-6	*	*
* None found.						

Directions, Recommendations, and Suggestions Regarding Proposed Use
We are asking FDA to prescribe a zero tolerance as the most appropriate condition of use of the substances described above as flavors. We are not addressing their use as indirect additives or food contact substances at this time. We are proposing only that they not be used as a flavor in food.

Data establishing that food additive will have intended physical or other technical effect
We are asking FDA to prescribe a zero tolerance as the most appropriate condition of use of the substances described above as flavors. A flavor or flavor extract is not essential to the function of food.

Description of practicable methods to determine the amount of the food additive in the food
We are asking FDA to prescribe a zero tolerance as the most appropriate condition of use of the substances described above as flavors. If they are not added, there need be no practical methods to determine the amount added.

Full reports of investigations made with respect to the safety of the food additive
See Appendix 3.

Proposed tolerances for the food additive
We are asking FDA to prescribe a zero tolerance as the most appropriate condition of use of the substances described above as flavors. As a result, no tolerance is needed.

Full information on each proposed change to the original regulation
See Appendix 4 for the specific changes requested to 21 CFR § 172.515. Text in strikethrough font is to be deleted.

Environmental impact statement
The proposed action complies with the categorical exclusion criteria pursuant to 40 CFR § 1508.4. No extraordinary circumstances as defined at 21 CFR § 25.21 exist for the action requested in this petition which would require the submission of an Environmental Assessment.

A food manufacturer may determine that the flavor additive is not essential and choose not to replace it. We could identify no extraordinary circumstances that would result from this removal without replacement.

Should the manufacturer determine that another flavor additive were needed to replace one of the eight synthetic flavor substances covered by this petition, it would likely turn to 21 CFR § 172.515 to identify alternatives. While most of those hundreds of alternative food additives were approved by FDA before the National Environmental Policy Act was adopted and have not been reassessed by the agency for their current risk, we did not identify a potential for serious harm to the environment or protected species that compares to the risk posed by the use of these alternatives.

If the manufacturer determined that these additives were also insufficient and no additives were "generally recognized as safe" without FDA review, the manufacturers would submit a food additive petition for agency review. In this review, the agency would consider compliance with the National Environmental Policy Act.

Appendix 3
Reports on the Carcinogenicity of the Eight Flavor Additives

We are asking FDA to prescribe a zero tolerance as the most appropriate condition of the use of the additives based on the Delaney Clause which applies to food additives and GRAS substances such as flavors. According to 21 U.S.C. § 348(c) regarding FDA's approval or denial of this petition,

"(1) The Secretary shall--
  (A) by order establish a regulation (whether or not in accord with that proposed by the petitioner) prescribing, with respect to one or more proposed uses of the food additive involved, the conditions under which such additive may be safely used (including, but not limited to, specifications as to the particular food or classes of food in or in which such additive may be used, the maximum quantity which may be used or permitted to remain in or on such food, the manner in which such additive may be added to or used in or on such food, and any directions or other labeling or packaging requirements for such additive deemed necessary by him to assure the safety of such use), and shall notify the petitioner of such order and the reasons for such action; or
  (B) by order deny the petition, and shall notify the petitioner of such order and of the reasons for such action.

(2) The order required by paragraph (1)(A) or (B) of this subsection shall be issued within ninety days after the date of filing of the petition, except that the Secretary may (prior to such ninetieth day), by written notice to the petitioner, extend such ninety-day period to such time (not more than one hundred and eighty days after the date of filing of the petition) as the Secretary deems necessary to enable him to study and investigate the petition.

(3) No such regulation shall issue if a fair evaluation of the data before the Secretary—
  (A) fails to establish that the proposed use of the food additive, under the conditions of use to be specified in the regulation, will be safe: *Provided,* **That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal**, except that this proviso shall not apply with respect to the use of a substance as an ingredient of feed for animals which are raised for food production, if the Secretary finds (i) that, under the conditions of use and feeding specified in proposed labeling and reasonably certain to be followed in practice, such additive will not adversely affect the animals for which such feed is intended, and (ii) that no residue of the additive will be found (by methods of examination prescribed or approved by the Secretary by regulations, which regulations shall not be subject to subsections (f) and (g)) in any edible portion of such animal after slaughter or in any food yielded by or derived from the living animal;
  (B) shows that the proposed use of the additive would promote deception of the consumer in violation of this Act [21 USCS §§ 301 et seq.] or would otherwise result in adulteration or in misbranding of food within the meaning

of this Act [21 USCS §§ 301 et seq.].” (21 U.S.C. § 348(c)(1)-(3)) (*Emphasis added*).

Under the Delaney Clause, if an additive is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal, it is not safe and must not be allowed to be intentionally added to food.

We understand from FDA that some in the agency and in industry maintain that the Delaney Clause does not apply to GRAS substances. These individuals claim that if a chemical is found to induce cancer when ingested by man or animal, it may be intentionally added to food as GRAS even if it could never be approved as a food additive. This position is untenable under the law. Were it to apply, a food additive that would be disallowed under Delaney would be permissible as long as the manufacturer secretly or publically characterized the substance as “GRAS,” whether generally or for that condition of use. Thus, GRAS would be an easy route for carcinogenic substances to avoid the explicit ban on carcinogenic food additives established by Congress. Yet as the design of the statute makes clear, Congress would never have intended to hold GRAS substances, as the target of less regulation and the subject of general knowledge of safety, to a less onerous safety standard than food additives.

Rather, as the legislative history amply demonstrates,[29] Congress intended most new and potentially dangerous substances to receive more exacting review by FDA under the food additive petition process. Carcinogenic substances, as specifically highlighted by the Delaney Clause, certainly belong in such a category. Thus, any likely carcinogens must necessarily be assessed as food additives, subject to the Delaney Clause, even if they were once considered GRAS.[30]

Our view is consistent with FDA’s own regulations. FDA regulations expressly state that the same safety standard applies to food additives and GRAS substances. Under the current regulations, GRAS status based on scientific procedures “require[s] the same quantity and quality of scientific evidence as is required to obtain approval of a food additive regulation for the ingredient.”[31] FDA has further clarified that a GRAS substance is “neither more safe nor less safe than approved food additives.”[32] Instead, a GRAS substance is distinguished from a food additive only on the basis of the degree of *common knowledge* about the safety of the substance.[33] This means that, applying FDA’s own regulations, the Delaney Clause *must* apply to GRAS substances, because such substances cannot be less safe than food additives.

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[29] For an in-depth discussion of the legislative history of the Food Additive Amendment of 1958, see Comment by Center for Science in the Public Interest (CSPI), Consumers Union, Environmental Working Group (EWG), and Natural Resources Defense Council (NRDC) re: Substances Generally Recognized as Safe, available at http://cspinet.org/new/pdf/GRAS%20Comment%20FINAL.pdf.

[30] Moreover, if Delaney did not apply to GRAS, any independent GRAS determinations by manufacturers of likely carcinogens would be plainly insufficient to support a “general recognition of safety,” as neither FDA nor the food industry currently collects or reports on the cumulative effects information necessary to address the safety of any condition of use.

[31] 21 C.F.R. § 170.30(b).

[32] Substances Generally Recognized as Safe, 62 Fed. Reg. 18938, 18942 (Apr. 17, 1997).

[33] *Id.* at 18940.

Therefore, our analysis of the safety of the eight flavors solely addresses whether the flavor additives are prohibited based on the Delaney Clause. The extent of exposure is not a factor.

We believe this finding should rest on conclusions by recognized authorities responsible for determining whether a substance is found to induce cancer when ingested by man or animal. We started by looking at FDA's evaluation. It approved the synthetic flavors as food additives in 1964 before the evidence that the flavors induced cancer became available. We have been unable to find any evidence that FDA reassessed the safety of any of the eight flavors in light of the cancer findings. We also looked for reassessments by FEMA.

Part I: Evaluation Organized by Recognized authority

We also looked at the recognized authorities responsible for determining whether a chemical is found to induce cancer in man or animals. We identified three such authorities that have evaluated the flavors listed on Table 1 for carcinogenicity. Each used a transparent process that provided an opportunity for scientists and other stakeholders to weigh in on the decision. The three recognized authorities are:

A. National Toxicology Program Report on Carcinogens

Since 1978, Congress has directed the program in the National Institutes of Health to publish a report identifying carcinogens, known as the Report on Carcinogens (ROC). The most recent ROC is the 13th edition issued in October 2014.[34]

NTP has designated two synthetic flavors, **methyl eugenol** and **styrene**, as **"reasonably anticipated to be human carcinogen."** This designation means there is either:

1. Limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded; or
2. Sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset; or
3. Less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.[35]

[34] NTP, 13th Report on Carcinogens, 2014. See http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.
[35] Id at p 2.

B. National Toxicology Program Cancer Studies

Since NTP's findings were based on ingestion studies done consistent with FDA's Redbook.[36] NTP made these findings pursuant to a Congressional directive at 42 U.S.C. § 241 to the HHS Secretary to conduct these types of tests. The Secretary established NTP to perform this work.

Congress also mandated at 42 U.S.C. § 241(b)(4) that the Secretary publish a biennial report listing substances: 1) which are known to be carcinogens or may reasonably be anticipated to be carcinogens, and 2) to which a significant number of persons residing in the United States are exposed. With the Secretary's approval, NTP has designated two of these eight synthetic flavors additives, **methyl eugenol and styrene**, as "reasonably anticipated to be a human carcinogen" in its biennial report known as the Report on Carcinogens.[37]

C. International Agency for Research on Cancer (IARC)

IARC is the science program of the World Health Organization (WHO) launched in 1965 to provide critical reviews and evaluations of evidence on the carcinogenicity of a wide range of human exposures.[38] It publishes Monographs on the Evaluation of Carcinogenic Risks to Humans. The most recent monograph was Volume 108 published in 2014.[39] Since it is part of WHO, we consider IARC to be a recognized authority.

IARC designated six synthetic flavors**, benzophenone, ethyl acrylate, methyl eugenol, pulegone, styrene and *trans,trans*-2,4-hexadienal,** to be **"possibly carcinogenic to humans"** in class 2B. For five of these flavors the agency concluded that there was sufficient evidence in experimental animals for the carcinogenicity. For styrene, it found limited evidence of carcinogenicity in both humans and experimental animals but assigned it class 2B based on the cumulative evidence. IARC reached this conclusion in 2000 and did not have the benefit of studies published after 2000 that resulted in NTP reaching a stronger conclusion.

IARC listed a seventh, beta-myrcene, as priority for monograph in the 2015-2019 period.[40] IARC has not considered pyridine since NTP published its definitive study in 2000.

This designation means:

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[36] FDA, Guidance for Industry and Other Stakeholders: Toxicology Principles for the Safety Assessment of Food Ingredients (Redbook 2000), 2007. Chapter IV.C.6. Accessed May 23, 2015. See http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm.

[37] NTP, Report on Carcinogens, Thirteenth Edition, 2014. See http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html.

[38] IARC, Preamble to the Monographs, accessed on 2/21/15 at http://monographs.iarc.fr/ENG/Preamble/currenta1background0706.php

[39] IARC, Monographs and Supplements Available Online, accessed on 2/21/15 at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php.

[40] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, INTERNAL REPORT 14/002, Report of the Advisory Group to Recommend Priorities for IARC Monographs during 2015–2019, 2014. http://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf.

1. This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals.
2. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals.
3. In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.[41]

D. California's Proposition 65 (California) OEHHA

The Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65,[42] is a regulatory program designed to protect California's citizens and its drinking water sources from chemicals known to cause cancer, birth defects, or other reproductive harm, and to inform citizens about exposures to such chemicals. The Office of Environmental Health Hazard Assessment (OEHHA) manages Proposition 65. Through a process that includes public notice and an opportunity to comment, OEHHA has designated seven of the eight synthetic flavors as carcinogens and has proposed this designation for the eighth. A chemical is designated a **carcinogen** by one of four methods:

1. A committee of independent scientists known as the Carcinogen Identification Committee (CIC)[43] is part of OEHHA's Science Advisory Board. The committee members are appointed by the Governor and are designated as the "State's Qualified Experts" for evaluating chemicals under Proposition 65. When determining whether a chemical should be placed on the list, the committees base their decisions on the most current scientific information available. OEHHA staff scientists compile all relevant scientific evidence on various chemicals for the committees to review. The committees also consider comments from the public before making their decisions. OEHHA designated **ethyl acrylate** as carcinogen through this method.
2. An organization designated as an "authoritative body" by the CIC has identified it as causing cancer. The following organizations have been designated as authoritative bodies: the U.S. Environmental Protection Agency (EPA), U.S. Food and Drug Administration (U.S. FDA), National Institute for Occupational Safety and Health, NTP and IARC. OEHHA designated three of the eight synthetic flavors, **methyl eugenol, pyridine, and *trans,trans*-2,4-hexadienal**, as carcinogens through this method. On February 27, 2015, it proposed listing **styrene** as a carcinogen; as of May 23, 2015, the agency has not made a final decision.
3. An agency of the state or federal government requires that it be labeled or identified as causing cancer or birth defects or other reproductive harm. Most chemicals listed in this manner are prescription drugs that are required by the U.S. FDA to contain warnings relating

[41] IARC, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Preamble, (2006) p 23. See http://monographs.iarc.fr/ENG/Preamble/CurrentPreamble.pdf.
[42] OEHHA, Proposition 65, accessed on May 23, 2015 at http://www.oehha.ca.gov/prop65.html.
[43] OEHHA, Proposition 65, Science Advisory Board Carcinogen Identification Committee, accessed May 23, 2015 at http://www.oehha.ca.gov/prop65/policy_procedure/CICmembers.html.

to cancer or birth defects or other reproductive harm. None of the eight flavors were designated as carcinogens through this method.

4. The California Labor Code list of chemicals meeting certain scientific criteria and identified as causing cancer or birth defects or other reproductive harm. This method established the initial chemical list following voter approval of Proposition 65 in 1986 and continues to be used as a basis for listing as appropriate.[44] OEHHA designated two of the eight synthetic flavors, **benzophenone** and **pulegone,** through this method.

Part II: Evaluations Organized by Carcinogenic Flavor

We incorporate the referenced findings of the recognized authorities as well as the FEMA Expert Panel's analysis by reference and summarize them below for each of the eight flavor additives.

A. Benzophenone / Diphenylketone (CAS No. 119-61-9)

FEMA's Expert Panel determined benzophenone to be GRAS at average maximum use levels of 0.5 to 2.4 ppm, assigned it FEMA No. 2134, and published its conclusion in 1965 as part of FEMA's GRAS 3 report.[45] The specific average maximum use levels are: baked goods at 2.4 ppm; ice cream, ices etc. at 0.61 ppm; beverages at 0.5 ppm; and candy at 1.7 ppm. A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[46] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

In 2012, California's OEHHA designated benzophenone as a carcinogen[47] based on IARC's article in Lancet designating the chemical as a 2B carcinogen.[48]

In 2006, in response to a study it conducted, NTP stated that "We conclude that benzophenone caused kidney cancer in male rats, liver tumors in male mice, and histiocytic sarcomas in female mice. Benzophenone may also have been associated with development of leukemia in male and female rats and with liver tumors in female mice."[49]

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[44] OEHHA, Proposition 65 in Plain Language, accessed on 2/21/15 at http://www.oehha.ca.gov/prop65/background/p65plain.html.

[45] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.

[46] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).

[47] OEHHA, Chemicals Listed Effective June 22, 2012 As Known To The State Of California To Cause Cancer: benzophenone (CAS No. 119-61-9), coconut oil diethanolamine condensate (cocamide diethanolamine) (CAS No. 68603-42-9), diethanolamine (CAS No. 111-42-2), and 2-methylimidazole (CAS No. 693-98-1), June 22, 2012. See http://oehha.ca.gov/prop65/prop65_list/062212list.html.

[48] Grosse Y, Baan R, Secretan-Lauby B, El Ghissassi F, Bouvard V, Benbrahim-Tallaa L, Guha N, Islami F, Galichet L, Straif K, on behalf of the WHO International Agency for Research on Cancer Monograph Working Group (2011). Carcinogenicity of chemicals in industrial and consumer products, food contaminants and flavourings, and water chlorination byproducts. *Lancet Oncology* **12**(4):328-9. [URL: http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045%2811%2970088-2/fulltext]

[49] NTP, Technical Report on the Toxicology and Carcinogenesis Studies of Benzophenone (CAS No 119-61-9) in F33/N Rats and B6C3F1 Mice (Feed Studies), 2006. See http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr533.pdf.

NTP went on to explain that:

> Under the conditions of these 2-year studies, there was *some evidence of carcinogenic activity** of benzophenone in male F344/N rats based on increased incidences of renal tubule adenoma; mononuclear cell leukemia in male F344/N rats may have been related to benzophenone exposure. There was *equivocal evidence of carcinogenic activity* of benzophenone in female F344/N rats based on the marginally increased incidences of mononuclear cell leukemia and histiocytic sarcoma. There was *some evidence of carcinogenic activity* of benzophenone in male $B6C3F_1$ mice based on increased incidences of hepatocellular neoplasms, primarily adenoma. There was *some evidence of carcinogenic activity* of benzophenone in female $B6C3F_1$ mice based on increased incidences of histiocytic sarcoma; the incidences of hepatocellular adenoma in female $B6C3F_1$ mice may have been related to benzophenone exposure.[50]
>
> Administration of benzophenone in feed resulted in increased incidences and/or severities of nonneoplastic lesions in the kidney and liver of male and female rats and in the liver, kidney, nose, and spleen of male andfemale mice. [51]

In 1999, IARC designated benzophenone as "Possibly Carcinogenic to Humans (2B)" based on its analysis of mouse and rat studies.[52] It stated that:

> Benzophenone was tested for carcinogenicity by oral administration in the diet in one study in mice and rats and by dermal application in one study in mice. Oral administration of benzophenone significantly increased the incidence of hepatocellular adenoma, and hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma (combined) in male mice and histiocytic sarcoma in female mice. It increased the incidence of mononuclear-cell leukaemia in male and female rats (not statistically significant in females), renal tubule adenoma in male rats and histiocytic sarcoma in female rats (not statistically significant). Dermal application of benzophenone did not induce tumours in mice. Tumours of the kidney, histiocytic sarcomas and hepatoblastomas are rare spontaneous neoplasms in experimental animals.[53]

IARC concluded that "There is *sufficient evidence* in experimental animals for the carcinogenicity of benzophenone." [54]

B. Ethyl Acrylate (CAS No. 140-88-5)

A FEMA Expert Panel determined ethyl acrylate to be GRAS at average maximum use levels of 0.06 to 1.1 ppm, assigned it FEMA No. 2418, and published its conclusion in 1965 as part of

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[50] Id.
[51] Id.
[52] IARC, Benzophenone, IARC Monograph – Volume 101-007, 2012, pp. 285-304. See http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-007.pdf.
[53] Id.
[54] Id.

FEMA's GRAS 3 report.[55] The specific average maximum use levels are: candy and baked goods at 1.1 ppm; beverages at 0.13-0.26 ppm; ice cream, ices etc. at 0.06-1 ppm; and chewing gum at 0.1 ppm. A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[56] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

In 1999, IARC designated ethyl acrylate as "Possibly Carcinogenic to Humans (2B)"[57] It stated that:

> Ethyl acrylate was tested for carcinogenicity by oral gavage in mice and rats. Dose-related increases in the incidence of squamous-cell papillomas and carcinomas of the forestomach were observed in both species. Ethyl acrylate was tested by inhalation in the same strains of mice and rats; no treatment-related neoplastic lesion was observed. No treatment-related tumour was observed following skin application of ethyl acrylate for lifespan to male mice (IARC, 1986).[58]

Regarding the rat studies, IARC stated that:

> Three groups of 25 male Fischer 344 rats, two months of age, were treated with 200 mg/kg bw ethyl acrylate (purity, 99%) by gavage in corn oil on five days per week for six or 12 months. Control rats received 5 mL corn oil/kg bw per day on five days per week for 12 months. Five rats from each treatment group were killed 24 h after the last dose. The remaining rats were killed at 24 months of age. All animals were examined for gross lesions and the stomachs were collected and fixed in formalin. Microscopic examination was restricted to three or four sections of the stomach. No treatment-related neoplastic lesions were observed in the forestomach of rats exposed to ethyl acrylate for six months and autopsied at 24 months of age. After 12 months of ethyl acrylate administration, all rats showed hyperplastic lesions but no neoplastic lesions were detected. However, when rats received ethyl acrylate for 12 months and were killed after nine months of recovery, they developed squamous-cell carcinomas (3/13) and papillomas (1/13) (Ghanayem *et al*., 1993). [The Working Group noted that histopathological evaluation was limited to the stomach.][59]

IARC concluded that "There is *sufficient evidence* in experimental animals for the carcinogenicity of ethyl acrylate." [60]

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[55] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.
[56] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).
[57] IARC, Ethyl Acrylate, IARC Monograph – Volume 71-99, 1999, pp. 1447-1457. See http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-99.pdf.
[58] Id.
[59] Id.
[60] Id.

In 1989, California's OEHHA designated ethyl acrylate as a carcinogen based on the analysis of its independent committee of cancer expert.[61]

In 1986, in response to a study it conducted, NTP stated "Under the conditions of these studies, ethyl acrylate was carcinogenic for the forestomach of F344/ N rats and B6C3F1 mice, causing squamous cell carcinomas in male rats and male mice, squamous cell papillomas in male and female rats and male mice, and squamous cell papillomas or carcinomas (combined) in male and female rats and mice. Evidence for carcinogenicity was greater in males than in females. Ethyl acrylate also caused irritation of the forestomach mucosa in male and female rats and mice."[62]

C. Eugenyl methyl ether / 4-Allylveratrole / Eugenyl Methyl Ether (CAS No. 93-15-2)

FEMA Expert Panel determined methyl eugenol (also known as eugenyl methyl ether) to be GRAS at average maximum use levels of 4.8 to 52 ppm, assigned it FEMA No. 2476, and published its conclusion in 1965 as part of FEMA's GRAS 3 report.[63] The specific average maximum use levels are: jellies at 52 ppm; baked goods at 13 ppm; candy at 11 ppm; beverages at 10 ppm; and ice cream, ices etc. at 4.8 ppm. A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[64] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

In 2004, IARC designated methyl eugenol as "Possibly Carcinogenic to Humans (2B)."[65] It stated that:

> Methyl eugenol was tested for carcinogenicity by oral administration by gavage in one study in mice and one study in rats and by intraperitoneal administration to mice in one study. In mice, oral administration of methyl eugenol caused a significantly increased incidence of liver tumours (hepatocellular adenoma, hepatocellular carcinoma and hepatoblastoma) in both sexes. In rats, oral administration of methyl eugenol caused a significantly increased incidence of liver tumours (hepatocellular adenoma, hepatocellular carcinoma, hepatocholangioma and hepatocholangiocarcinoma) and benign and malignant neuroendocrine tumours of the glandular stomach in males and females, and renal tubule adenoma of the kidney, mammary gland fibroadenoma, skin fibroma, skin fibroma or fibrosarcoma (combined) and mesothelioma in males in the main and stop-exposure experiments. Tumours of the kidney, fibromas and fibrosarcomas of the skin, mesotheliomas, hepatoblastomas and hepatocholangiocarcinomas are rare spontaneous neoplasms, and neuroendocrine tumours of the glandular stomach are extremely rare spontaneous neoplasms in experimental animals. In the main and stop-

[61] OEHHA, Chemicals Listed Effective November 4, 2011 as Known to the State of California to Cause Cancer: Five Chemicals, November 4, 2011. See http://oehha.ca.gov/prop65/docs_admin/110411LClist.html.
[62] NTP, Carcinogenesis Studies of Ethyl Acrylate (CAS No. 140-88-5) in F344 Rats and B6C3F1 Mice (Gavage Studies), 1986. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr200299/abstracts/tr259/index.html.
[63] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.
[64] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).
[65] IARC, Methyl Eugenol, IARC Monograph – Volume 101-013, 2012, pp. 407-433. See http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-013.pdf.

> exposure experiments in rats, there was consistency in the tumour response for cancers of the liver and glandular stomach in males and females, and of the kidney in males.[66]

IARC also stated that "Intraperitoneal injection of methyl eugenol caused a significantly increased incidence of hepatocellular adenoma in male mice. 1′-Hydroxymethyleugenol, a metabolite of methyl eugenol, was tested for carcinogenicity by intraperitoneal injection in one study in mice, and caused a significantly increased incidence of hepatocellular adenoma in males."[67]

IARC concluded that "There is *sufficient evidence* in experimental animals for the carcinogenicity of methyleugenol."[68]

In 2002, NTP designated methyl eugenol to be "Reasonably Anticipated To Be Human Carcinogen."[69] In its 13th Report on Carcinogens published in 2014, NTP stated that:

> Methyl eugenol is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals." Regarding cancer studies in experimental animals it said "Oral exposure to methyl eugenol caused tumors in two rodent species and at several different tissue sites. Methyl eugenol administered by stomach tube caused benign or malignant liver tumors (hepatocellular adenoma or carcinoma) in rats and mice of both sexes. In rats, methyl eugenol also caused benign or malignant stomach tumors (neuroendocrine tumors) in both sexes and tumors of the kidney (renal-tubule adenoma), mammary gland (fibroadenoma), and skin (fibroma or fibrosarcoma) in males. Malignant neuroendocrine tumors of the stomach in male mice also were considered to be related to methyl eugenol exposure (NTP 2000). Earlier studies found that methyl eugenol and two structurally related allylbenzenes, safrole and estragole, caused liver tumors in mice when administered by intraperitoneal injection (IARC 1976, Miller *et al.* 1983). Safrole is listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen* and by the International Agency for Research on Cancer as possibly carcinogenic to humans.[70]

NTP evaluated studies on the mechanisms of carcinogenesis and stated:

> Mechanistic studies indicate that liver tumors induced by methyl eugenol and structurally related allylbenzenes result from metabolism of these compounds to DNA-reactive intermediates. Methyl eugenol may be bioactivated by three different pathways: (1) hydroxylation at the 1′ position of the allylic side chain to yield 1′-hydroxymethyleugenol, followed by sulfation of this intermediate to form 1′-hydroxymethyleugenol sulfate, (2) oxidation of the 2′,3′-double bond of the allylic side chain to form methyleugenol-2,3-oxide, and (3) O-demethylation followed by spontaneous rearrangement to form eugenol quinone methide. Formation of protein

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[66] Id.
[67] Id.
[68] Id.
[69] NTP, Report on Carcinogens, Thirteenth Edition, Methyleugenol, 2014. See http://ntp.niehs.nih.gov/go/roc13.
[70] Id.

> adducts and DNA adducts in the livers of animals (and in cultured human hepatocytes) exposed to allylbenzenes and induction of liver tumors by these compounds in animals have been attributed to activation via the hydroxylation pathway, because similar effects were produced by the 1′-hydroxy metabolites and because these effects were inhibited by pretreatment with sulfotransferase inhibitors (Boberg *et al.* 1983, Miller *et al.* 1983, Randerath *et al.* 1984, Gardner *et al.* 1996, NTP 2000).[71]

NTP further said:

> Methyl eugenol, safrole, and estragole caused unscheduled DNA synthesis in rat hepatocytes, and their corresponding 1′-hydroxy metabolites were more potent genotoxic agents than were the parent compounds (Howes *et al.* 1990, Chan and Caldwell 1992). Methyl eugenol caused morphological transformation of Syrian hamster embryo cells (Kerckaert *et al.* 1996), sister chromatid exchange in Chinese hamster ovary (CHO) cells (NTP 2000), intrachromosomal recombination in yeast (Schiestl *et al.* 1989), and DNA repair in *Bacillus subtilis* (Sekizawa and Shibamoto 1982). It did not cause mutations in *Salmonella typhimurium* (NTP 2000) or *Escherichia coli* (Sekizawa and Shibamoto 1982), chromosomal aberrations in CHO cells (NTP 2000), or micronucleus formation in the peripheral-blood erythrocytes of mice (NTP 2000). A higher frequency of b-catenin mutations was observed in liver tumors from mice exposed to methyl eugenol than in spontaneous liver tumors from unexposed mice (Devereux *et al.* 1999). Methyl eugenol's lack of mutagenicity in bacteria may be due to the need for sulfation in the metabolic activation of methyl eugenol to its ultimate mutagenic or carcinogenic form.[72]

In 2001, California's OEHHA designated methyl eugenol as a carcinogen based on NTP's study saying that NTP "concluded that there is clear evidence of the carcinogenic activity of methyleugenol in male and female F344/N rats and in male and female B6C3F1 mice."[73]

In 2000, in response to a study it conducted, NTP stated:

> Under the conditions of these 2-year gavage studies, there was clear evidence of carcinogenic activity* of methyleugenol in male and female F344/N rats based on the increased incidences of liver neoplasms and neuroendocrine tumors of the glandular stomach in male and female rats and the increased incidences of kidney neoplasms, malignant mesothelioma, mammary gland fibroadenoma, and subcutaneous fibroma and fibroma or fibrosarcoma (combined) in male rats. A marginal increase in the incidence of squamous cell neoplasms of the forestomach may have been related to methyleugenol administration in female rats. There was clear evidence of carcinogenic activity of methyleugenol in male and female B6C3F$_1$ mice based on the increased incidences of

[71] Id.
[72] Id.
[73] OEHHA, Chemical Listed Effective November 16, 2001 as Known to the State of California to Cause Cancer: Methyleugenol, November 16, 2001. See http://oehha.ca.gov/prop65/out_of_date/pdf_zip/11-16NOT.pdf.

> liver neoplasms. Neuroendocrine tumors of the glandular stomach in male mice were also considered related to methyleugenol administration.[74]

NTP further found, "[i]n male and female rats and mice, methyleugenol administration caused significant increases in the incidences of nonneoplastic lesions of the liver and glandular stomach."[75]

In 2002, the FEMA Expert Panel reaffirmed that methyl eugenol was generally recognized as safe.[76] While not disputing OEHHA's conclusion that it was a carcinogen, the Panel stated that the:

> hazard determination uses a mechanism-based approach in which production of the hepatotoxic sulfate conjugate of the 10-hydroxy metabolite is used to interpret the pathological changes observed in different species of laboratory rodents in chronic and subchronic studies. In the risk evaluation, the effect of dose and metabolic activation on the production of the 10-hydroxy metabolite in humans and laboratory animals is compared to assess the risk to humans from use of methyl eugenol and estragole as naturally occurring components of a traditional diet and as added flavouring substances. Both the qualitative and quantitative aspects of the molecular disposition of methyl eugenol and estragole and their associated toxicological sequelae have been relatively well defined from mammalian studies. Several studies have clearly established that the profiles of metabolism, metabolic activation, and covalent binding are dose dependent and that the relative importance diminishes markedly at low levels of exposure (i.e. these events are not linear with respect to dose). In particular, rodent studies show that these events are minimal probably in the dose range of 1-10 mg/kg body weight, which is approximately 100–1000 times the anticipated human exposure to these substances. For these reasons it is concluded that present exposure to methyl eugenol and estragole resulting from consumption of food, mainly spices and added as such, does not pose a significant cancer risk. Nevertheless, further studies are needed to define both the nature and implications of the dose–response curve in rats at low levels of exposure to methyl eugenol and estragole.[77]

In essence, FEMA says that despite methyl eugenol causing cancer in an animal, the cancer risk is not significant enough. This analysis is inconsistent with the Delaney Clause.

D. Myrcene / 7-methyl-3-methylene-1,6-octadiene (CAS No. 123-35-3)

A FEMA Expert Panel determined myrcene to be GRAS at an average maximum use level of 13 ppm in candy, 6.4 ppm in ice cream, ices, etc., 4.9 ppm in baked goods, and 4.4 ppm in

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[74] NTP, Carcinogenesis Studies of Methyl Eugenol (CAS No. 93-15-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2000. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr400499/abstracts/tr491/index.html.
[75] Id.
[76] R.L. Smith, T.B. Adams, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, W.J. Waddell, B.M. Wagner, A.E. Rogers, J. Caldwell, I.G. Sipes, Safety assessment of allylalkoxybenzene derivatives used as flavouring substances — methyl eugenol and estragole, Food and Chemical Toxicology 40 (2002) 851–870.
[77] Id.

beverages, assigned it FEMA No. 2762, and published its conclusion in 1965 as part of FEMA's GRAS 3 report. [78]

In 2014, California's OEHHA designated beta-myrene to be a carcinogen based on the NTP study conducted in 2010.[79]

In 2011, in response to a study it conducted, NTP stated "We conclude that β-myrcene caused kidney cancers in male rats and liver cancer in male mice, and the occurrence of kidney tumors in female rats and liver tumors in female rats may have been related to β-myrcene administration. In addition β-myrcene was associated with other lesions of the kidney in rats, the liver in mice, and the nose in male rats."[80]

NTP concluded that there was clear evidence of carcinogenic activity of beta-myrcene in male F344/N rats and male B6C3F$_1$ mice.[81]

E. Pulegone / p- Menth-4(8)-en-3-one (CAS No. 89-82-7)

A FEMA Expert Panel determined pulegone to be GRAS at average maximum use levels of 5 to 25 ppm, assigned it FEMA No. 2731, and published its conclusion in 1965 as part of FEMA's GRAS 3 report.[82] The specific average maximum use levels are: baked goods at 24-25 ppm; candy at 17 ppm; ice cream, ices etc. at 5-32 ppm; and beverages at 5-8 ppm. A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[83] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

In 2014, IARC designated pulegone as "Possibly Carcinogenic to Humans (2B)" saying "There is *sufficient evidence* in experimental animals for the carcinogenicity of pulegone."[84] Regarding the animal carcinogenicity data, IARC stated that

> Pulegone was tested for carcinogenicity after oral administration in one study in mice and one study in rats. In male and female mice given pulegone by gavage, there was a

[78] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.
[79] OEHHA, Chemical Listed Effective March 27, 2015 as Known to the State of California to Cause Cancer: Beta-Myrcene, 2015. See http://oehha.ca.gov/prop65/CRNR_notices/list_changes/032415listbetamyrcene.html.
[80] NTP, Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2010. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr557/index.html.
[81] NTP, Toxicology and Carcinogenesis Studies of β-Myrcene (CAS No. 123-35-3) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2010. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr557/index.html.
[82] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.
[83] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).
[84] IARC, Pulegone, IARC Monograph – Volume 108-05, 2014, pp. 1-14. See http://monographs.iarc.fr/ENG/Monographs/vol108/mono108-05.pdf.

> significant increase in the incidences of hepatocellular adenoma, and hepatocellular adenoma and carcinoma (combined) in males and females, and of hepatoblastoma in males. In female mice, the incidence of osteoma or osteosarcoma (combined) was higher than that in historical controls. In female rats given pulegone by gavage, there was an increase in the incidence of urinary bladder papilloma and of urinary bladder papilloma or carcinoma (combined). In males, there were no treatment-related increases in tumour incidences.[85]

Regarding the mechanistic data, IARC stated that:

> Pulegone is readily absorbed in humans. It is metabolized in humans and rodents to isomers of hydroxypulegone, predominantly by hepatic oxidation at the 5-, 9-, and 10-positions. In rodents, 9-hydroxypulegone is further oxidized to menthofuran, which is converted to a reactive epoxide and a reactive aldehyde (γ-ketoenal). 5-Hydroxypulegone is converted to piperitenone, which is then hydroxylated at the 9-position and further converted to an analogous furan metabolite and to the γ-ketoenal. Further metabolism of the γ-ketoenal produces 4-methyl-2-cyclohexenone and *p*-cresol. Pulegone was not mutagenic in standard bacterial assays, either with or without exogenous metabolic activation. Studies in humans and rodents indicated that some of the pulegone metabolites deplete hepatic levels of glutathione and can bind to cellular proteins. This may result in chronic regenerative cell proliferation, which may be related to the carcinogenicity observed in the liver and urinary bladder in experimental animals.[86]

In 2014, California's OEHHA designated pulegone to be a carcinogen based on the IARC determination.[87]

In 2011, in response to a study it conducted, NTP stated "We conclude that pulegone caused cancer of the urinary bladder in female rats and cancer of the liver in male and female mice. Neoplasms of the bone in female mice were also possibly associated with administration of pulegone. There were no increases in cancers in male rats receiving pulegone. Pulegone also caused an unusual kidney lesion, hyaline glomerulopathy, in male and female rats and mice."[88]

NTP considered that there was clear evidence of carcinogenic activity of pulegone in female F344/N rats and male and female B6C3F$_1$ mice.[89]

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[85] Id.
[86] Id.
[87] OEHHA, NOTICE OF INTENT TO LIST PULEGONE BY THE LABOR CODE MECHANISM, February 7, 2014. See http://oehha.ca.gov/prop65/CRNR_notices/admin_listing/intent_to_list/noilLCset20pulegone.html.
[88] NTP, Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2011. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr563/index.html.
[89] NTP, Toxicology and Carcinogenesis Studies of Pulegone (CAS No. 89-82-7) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2011. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr500580/listedreports/tr563/index.html.

In 2005, the FEMA Expert Panel reaffirmed that pulegone was generally recognized as safe in its 22nd report on flavoring substances.[90] However, this analysis was done well before the 2011 studies upon which IARC based its conclusions.

F. Pyridine (CAS No. 110-86-1)

A FEMA Expert Panel determined pyridine to be GRAS at an average maximum use level of 0.02 to 1 ppm, assigned it FEMA No. 2731, and published its conclusion in 1965 as part of FEMA's GRAS 3 report.[91] The specific average maximum use levels are: beverages at 1 ppm; candy and baked goods at 0.4 ppm; and ice cream, ices etc. at 0.02-0.12 ppm. A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[92] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

In 2002, California's OEHHA designated pyridine as a carcinogen finding that there was an "Increased incidence of malignant tumors in male and female mice" based on an NTP study published in 2000.[93] It stated that NTP "concluded that there is clear evidence of carcinogenic activity of pyridine in male and female B6C3F1 mice."[94]

In 2000, IARC designated pyridine was "Not Classifiable as to its Carcinogenicity to Humans (Group 3)" based on NTP studies done in 1997 not the 2000 studies considered by OEHHA.[95]

In 2011, despite the conclusions of OEHHA, the FEMA Expert Panel reaffirmed that pyridine was generally recognized as safe in its 25nd report on flavoring substances.[96] The Panel based its decision upon pyridine's:

> efficient detoxification in humans; its low level of flavor use; the lack of genotoxic and mutagenic potential; the safety factor calculated from results of subchronic studies (NTP, 2000) indicating a margin of safety of at least 1,000; the conclusion that the statistically significant findings in the NTP mouse bioassay, of an increased incidence of hepatocellular neoplasms in male and female B6C3F1 mice were secondary to pronounced hepatotoxicity at high dose levels; the conclusion that the increased incidence of renal neoplasms in male F344/N rats occurs via a dose-dependent non-

[90] FEMA Expert Panel (R.L. Smith, S.M. Cohen, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, W.J. Waddell, B.M. Wagner, and T.B. Adams), GRAS Flavouring Substances 22 (FEMA No. 4069-4253), *Food Technology*, Vol. 59, No. 8, August 2005.
[91] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: III. GRAS Substances, (FEMA No. 2000-3124), *Food Technology*, Vol. 19, No. 2, 1965.
[92] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).
[93] OEHHA, Chemical Listed Effective May 17, 2002 as Known to the State of California to Cause Cancer: Pyridine, May 17, 2002. See http://oehha.ca.gov/prop65/out_of_date/51702notice.html.
[94] Id.
[95] IARC, Pyridine, IARC Monograph – Volume 77-16, 22000, pp. 503. http://www.inchem.org/documents/iarc/vol77/77-16.html.
[96] FEMA Expert Panel (R.L. Smith, W.J. Waddell, S.M. Cohen, S. Fukushima, N.J. Gooderham, S.S. Hecht, L.J. Marnett, P.S. Portoghese, I.M.C.M. Rietjens, T.B. Adams, C.L. Gavin, M.M. McGowen, and S.V. Taylor), GRAS Flavouring Substances 25 (FEMA No. 4667-4727), *Food Technology*, Vol. 65, No. 7, July 2011.

> genotoxic mode of action; and the conclusion that the increased incidence of mononuclear cell leukemia in female F344/N rats is likely species- and sex-specific, the biological significance of which remains uncertain. Based on these conclusions, the use of pyridine as a flavor ingredient is not considered to produce any significant risk to human health.[97]

In essence, FEMA says that despite methyl eugenol causing cancer in an animal, the cancer risk is not significant enough. This analysis is inconsistent with the Delaney Clause.

In 2000, in response to a study it conducted, NTP stated:

> Under the conditions of these 2-year drinking water studies, there was some evidence of carcinogenic activity* of pyridine in male F344/N rats based on increased incidences of renal tubule neoplasms. There was equivocal evidence of carcinogenic activity of pyridine in female F344/N rats based on increased incidences of mononuclear cell leukemia. There was equivocal evidence of carcinogenic activity in male Wistar rats based on an increased incidence of interstitial cell adenoma of the testis. There was clear evidence of carcinogenic activity of pyridine in male and female $B6C3F_1$ mice based on increased incidences of malignant hepatocellular neoplasms.[98]
>
> In F344/N rats, exposure to pyridine resulted in increased incidences of centrilobular cytomegaly and degeneration, cytoplasmic vacuolization, and pigmentation in the liver of males and females; periportal fibrosis, fibrosis, and centrilobular necrosis in the liver of males; and bile duct hyperplasia in females. In male Wistar rats, pyridine exposure resulted in increased incidences of centrilobular degeneration and necrosis, fibrosis, periportal fibrosis, and pigmentation in the liver, and, secondary to kidney disease, mineralization in the glandular stomach and parathyroid gland hyperplasia.[99]

G. Styrene (CAS No. 100-42-5)

A FEMA Expert Panel determined styrene to be GRAS at an average maximum use level of 0.2 ppm in ice cream, ices, candy, and baked goods, assigned it FEMA No. 3233, and published its conclusion in 1967 as part of FEMA's GRAS 4 report.[100] A year earlier, FDA approved the flavor as a food additive without establishing numerical maximum levels at 21 CFR §121.1164.[101] In 1977, FDA recodified this section without altering the requirements for the flavor to 21 CFR §172.515.

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[97] Id.
[98] NTP, Toxicology and Carcinogenesis Studies of Pyridine (CAS No. 110-86-1) in F344/N Rats, Wistar Rats, and $B6C3F_1$ Mice (Drinking Water Studies), 2000. http://ntp.niehs.nih.gov/results/pubs/longterm/reports/longterm/tr400499/abstracts/tr470/index.html.
[99] Id.
[100] R.L. Hall and B.L. Oser on behalf of FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: 4. GRAS Substances, (FEMA No. 3125-3249), *Food Technology*, Vol. 19, No. 2, 1965.
[101] FDA, Final Rule for Synthetic Flavoring Substances and Adjuvants, 29 Fed. Reg. 14625 (October 27, 1964).

In 2011, NTP designated styrene as "Reasonably Anticipated To Be Human Carcinogen" saying the chemical "is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting data on mechanisms of carcinogenesis."[102] In its 13th Report on Carcinogens published in 2014, NTP evaluated the limited evidence of carcinogenicity in humans stating that it is:

> based on studies of workers exposed to styrene that showed (1) increased mortality from or incidence of cancer of the lymphohematopoietic system and (2) increased levels of DNA adducts and genetic damage in lymphocytes from exposed workers. Elevated risks of lymphohematopoietic cancer were found among workers with higher exposure to styrene after an appropriate elapsed time since first exposure. In some studies, the risks increased with increasing measures of exposure, such as average exposure, cumulative exposure, or number of years since first exposure. However, the types of lymphohematopoietic cancer observed in excess varied across different cohort studies, and excess risks were not found in all cohorts. There is also some evidence for increased risks of esophageal and pancreatic cancer among styrene-exposed workers. Causality is not established, as the possibility that the results were due to chance or to confounding by exposure to other carcinogenic chemicals cannot be completely ruled out. However, a causal relationship between styrene exposure and cancer in humans is credible and is supported by the finding of DNA adducts and chromosomal aberrations in lymphocytes from styrene-exposed workers.[103]

Regarding animal studies, NTP stated:

> The evidence from studies in rats is insufficient for reaching a conclusion concerning the carcinogenicity of styrene. Lung tumors were not observed in rats (IARC 2002); however, findings for mammary-gland tumors were equivocal. The incidence of mammary-gland tumors was increased in female Sprague-Dawley rats exposed to styrene in the drinking water (mammary fibroadenoma; Huff 1984) or by inhalation (malignant tumors; Conti *et al.* 1988), but decreased incidences of mammary-gland tumors (adenocarcinoma) were reported in another inhalation-exposure study of rats of the same strain (Cruzan *et al.* 1998).[104]

Regarding the mechanisms of carcinogenesis, NTP stated that:

> Although styrene disposition differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard. Detection of styrene-7,8-oxide–DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action.[105]

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[102] NTP, Report on Carcinogens, Thirteenth Edition, Styrene, 2014. See http://ntp.niehs.nih.gov/go/roc13.
[103] Id.
[104] Id.
[105] Id.

In 2013, the U.S. District Court for the District of Columbia affirmed NTP's decision in the face of an industry challenge to the agency's determination. The court said "In short, the Report provides a rational explanation for the Secretary's decision to list styrene as a reasonably anticipated human carcinogen, and this explanation is adequately supported by the administrative record."[106]

In 2014, the National Research Council, at Congress' request,[107] reviewed NTP's assessment of styrene for the Report on Carcinogens. The NRC committee concluded that:

> NTP correctly determined that styrene should be considered for listing [as a carcinogen] in the RoC. There is sufficient evidence of exposure to a significant number of persons residing in the United States to warrant such consideration. NTP adequately documented that exposure to styrene occurs in occupational settings and in the general public regardless of smoking status.[108]
>
> After conducting a scientific review of the styrene assessment presented in the NTP 12th RoC, the committee finds that the overall conclusion reached by NTP in 2011, that styrene is "reasonably anticipated to be a human carcinogen," was appropriate. The following points of the listing criteria support NTP's conclusion:[109]
>
> - "There is limited evidence of carcinogenicity from studies in humans." Publications available to NTP as of June 10, 2011, provided limited but credible evidence that exposure to styrene is associated with lymphohematopoietic, pancreatic, and esophageal cancers. The most informative human epidemiologic studies that support that conclusion are those by Ruder et al. (2004), Wong et al. (1994), Kolstad et al. (1994), and Kogevinas et al. (1994). The evidence is limited in that chance, bias, or confounding factors could not be adequately excluded.[110]
>
> - "There is sufficient evidence of carcinogenicity from studies in experimental animals." Literature published by June 10, 2011, provided sufficient evidence that "there is an increased incidence of . . . a combination of malignant and benign tumors" in experimental animals induced by styrene administered by multiple routes of exposure (inhalation and oral gavage). The most informative experimental animal studies that support that conclusion are studies in mice (NCI 1979; Cruzan et al. 2001).[111]

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[106] U.S. District Court for the District of Columbia, Styrene Information and Research Center v. Sebelius, Civil Action 11-1079, 2013. Seehttps://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2011cv1079-56.

[107] 2012 Consolidated Appropriations Act (112th Congress, 1st Session; Public Law 112-74).

[108] National Research Council, Review of the Styrene Assessment in the National Toxicology Program 12th Report on Carcinogens, 2014. See http://www.nap.edu/catalog/18725/review-of-the-styrene-assessment-in-the-national-toxicology-program-12th-report-on-carcinogens.

[109] Id.

[110] Id.

[111] Id.

- "There is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans." Literature published by June 10, 2011, provided convincing evidence that genotoxicity is observed in cells from humans who were exposed to styrene. That evidence is derived from a large body of publications. In addition, styrene-7,8-oxide "was listed in a previous Report on Carcinogens as . . . reasonably anticipated as a human carcinogen." Styrene-7,8-oxide, a compound that is structurally related to styrene, is a major metabolite of styrene in both experimental animals and humans; it was first listed in the 10th RoC as reasonably anticipated to be a human carcinogen.[112]

In 2002, IARC designated styrene as "Possibly Carcinogenic to Humans (2B)."[113] Regarding the human studies, IARC stated:

> The increased risks for lymphatic and haematopoietic neoplasms observed in some of the studies are generally small, statistically unstable and often based on subgroup analyses. These findings are not very robust and the possibility that the observations are the results of chance, bias or confounding by other occupational exposures cannot be ruled out.[114]

Regarding animal carcinogenicity data, IARC stated:

> Styrene was tested for carcinogenicity in mice in one inhalation study and four oral gavage studies. In the inhalation study, in male mice there was an increase in the incidence of pulmonary adenomas and in female mice, there was an increase in the incidence of pulmonary adenomas, and only an increase in that of carcinomas in the high-dose group. Two of the gavage studies were negative. The other two were considered inadequate for an evaluation of the carcinogenicity of styrene. A screening study by intraperitoneal administration also did not find an increase in tumour incidence or multiplicity in mice. Styrene was tested for carcinogenicity in rats in four gavage studies, one drinking water study and two inhalation studies. Overall, there was no reliable evidence for an increase in tumour incidence in rats. Styrene 7,8-oxide is a major metabolite of styrene and has been evaluated previously (IARC, 1994b). The evaluation at that time was that there was sufficient evidence in experimental animals for the carcinogenicity of styrene 7,8-oxide.[115]

IARC concluded that "There is *limited evidence* in humans for the carcinogenicity of styrene" and "There is *limited evidence* in experimental animals for the carcinogenicity of styrene."[116] However, IARC's analysis, published in 2000 did not consider later studies that NTP relied upon to reach its determination.

H. *Trans,trans*-2,4-hexadienal (CAS No. 142-83-6)

[112] Id.
[113] IARC, Styrene, IARC Monograph – Volume 82-9, 2002, pp. 437-550. See http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf.
[114] Id.
[115] Id.
[116] Id.

A FEMA Expert Panel determined trans,trans-2,4-hexadienal to be GRAS at an average maximum use level of 6.3 ppm in beverages, ice cream, ices, candy, and baked goods, assigned it FEMA No. 3429, and published its conclusion in 1974 as part of FEMA's GRAS 8 report.[117] The specific average maximum use levels are: frozen desserts, confectionary, puddings, gelatins, jams, condiments, and pickles at 4 ppm; non-alcoholic beverages at 4 ppm; preserves and spreads at 2 ppm; and alcoholic beverages at 1 ppm.

In 2012, IARC designated 2,4-hexadienal as "Possibly Carcinogenic to Humans (2B)."[118] IARC stated that:

> 2,4-Hexadienal was tested for carcinogenicity by oral administration by gavage to mice and rats. In mice, it increased the incidence of forestomach squamous-cell papilloma and carcinoma in females, squamous-cell papilloma or carcinoma (combined) in males and females, and squamous-cell carcinoma of the tongue in males. In rats, oral administration of 2,4-hexadienal caused an increase in the incidence of forestomach squamous-cell papilloma in males and females, forestomach squamous-cell papilloma or carcinoma (combined) in males, and malignant pheochromocytoma of the adrenal gland in males. Tumours of the forestomach and the tongue are rare spontaneous neoplasms in experimental animals. [119]

IARC concluded that "There is *sufficient evidence* in experimental animals for the carcinogenicity of 2,4-hexadienal." [120]

If 2003, in response to studies it conducted, NTP stated that "We conclude that 2,4-hexadienal caused neoplasms of the forestomach in male and female rats and mice." [121] NTP considered that there was clear evidence of carcinogenic activity of 2,4-hexadienal in male and female F344/N rats and male and female B6C3F$_1$ mice. It also stated that the occurrence of squamous cell carcinoma of the oral cavity (tongue) in male B6C3F$_1$ mice may have been related to the administration of 2,4-hexadienal. NTP noted that the forestomach carcinogenic effect following administration of 2,4-hexadienal for 2 years occurred at lower doses than those at which an obvious irritative or inflammatory effect was observed in the 16-day and 14-week studies.[122]

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[117] B.L. Oser and R.A. Ford on behalf FEMA Expert Panel, Recent Progress in the Consideration of Flavouring Ingredients Under the Food Additives Amendment: 8. GRAS Substances, (FEMA No. 3424-3444), *Food Technology*, Vol. 28, No. 9, September 1974.
[118] IARC, 2,4-Hexadienal, IARC Monograph – Volume 101-012, 2012, pp. 391-405. See http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-012.pdf.
[119] Id.
[120] Id.
[121] NTP, Technical Report on the Toxicology and Carcinogenesis Studies of 2,4-Hexadienal (89% *trans,trans* isomer, CAS No. 142-83-6; 11% *cis,trans* isomer) in F344/N Rats and B6C3F1 Mice (Gavage Studies), 2003. See http://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr509.pdf.
[122] Id.

Later that year, the FEMA Expert Panel considered the 2003 NTP report and reaffirmed that 2,4-hexadienal was generally recognized as safe in its 21nd report on flavoring substances.[123] The Panel said:

> The appearance of forestomach hyperplasia and squamous cell papillomas in rodents is a regular occurrence in bioassay gavage studies in which high concentrations of an irritant material in corn oil is delivered daily by dosing tube into the forestomach. These phenomena are consistently associated with administration of high concentrations of aldehydes, e.g., malonaldehyde, furfural, benzaldehyde, and trans,trans-2,4-hexadienal (NTP 1988. 1990a. 1993a, 2001a) and other irritating substances, e.g., ethyl acrylate, dihydrocoumarin, and coumarin (NTP, 1990, 1992) in com oil by gavage. Squamous cell papillomas are benign lesions associated with squamous epithelium surfaces. A majority of papillomas arise as a result of chronic irritation or from infection from some strains of viruses (Smith and Ford, 1993). Given these results, high irritating concentrations of aldehyde administered by gavage over the lifetime of a rodent may progress to malignant neoplasms, as was observed in the high-dose group of female mice.[124]

The FEMA Panel continued:

> Apparently, the combination of daily introduction of a dosing tube into the forestomach and delivery of high concentrations of an irritating test material in com oil, which itself is a mild irritant and mitogen was in all probability, the source of the papillomas in the rodent forestomach. Gavage administration provides a bolus dose that exerts a traumatic effect on the forestomach epithelium. When repeated in chronic studies, it leads to chronic inflammation and regenerative hyperplasia. In contrast, the same total doses administered to rodents in the diet achieve maximum concentrations in the stomach and circulation that are significantly lower than those achieved by a bolus gavage dose. Therefore, the effects resulting from gavage administration would not be expected when 2,4-hexadienal is administered in the diet.[125]

The FEMA Panel further stated:

> This conclusion is supported by the observation that the occurrence of squamous cell papillomas and forestomach hyperplasia following gavage administration of an irritant in com oil for two years (NTR 1986a) do not develop when the same substance is administered at similar intake levels in the diet (NTP, 1993b). In addition, recent two-year bioassays performed with both aliphatic and aromatic aldehydes [trans-cinnamaldehyde and 3,7-dimethyl-2,6-octadienal (citral) 1administered microencapsulated in the diet at higher concentrations than those used in the gavage

[123] FEMA Expert Panel (R.L. Smith, S.M. Cohen, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, W.J. Waddell, B.M. Wagner, and T.B. Adams), GRAS Flavouring Substances 21 (FEMA No. 4024-4068), *Food Technology*, Vol. 57, No. 5, May 2003.
[124] Id.
[125] Id.

> studies mentioned above show no evidence of either forestomach hyperplasia, forestomach papillomas or forestomach carcinomas (NTP, 2001b, 2002).[126]

The FEMA does not appear to address the note by NTP forestomach carcinogenic effect occurred at lower doses than those at which an obvious irritative or inflammatory effect was observed in the 16-day and 14-week studies.[127]

[126] Id.
[127] Id.

Appendix 4
Requested changes to 21 CFR § 172.515

Note that we have removed chemicals from the table unaffected by this petition.

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)

PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION

Subpart F--Flavoring Agents and Related Substances

Sec. 172.515 Synthetic flavoring substances and adjuvants.

Synthetic flavoring substances and adjuvants may be safely used in food in accordance with the following conditions.

(a) They are used in the minimum quantity required to produce their intended effect, and otherwise in accordance with all the principles of good manufacturing practice.

(b) They consist of one or more of the following, used alone or in combination with flavoring substances and adjuvants generally recognized as safe in food, prior-sanctioned for such use, or regulated by an appropriate section in this part.

~~Benzophenone; diphenylketone.~~
~~Ethyl acrylate.~~
~~Eugenyl methyl ether; 4-allylveratrole; methyl eugenol.~~
~~Myrcene; 7-methyl-3-methylene-1,6-octadiene~~
~~Pulegone; *p*- menth-4(8)-en-3-one.~~
~~Pyridine.~~
~~Styrene.~~

(c) [Delta]-Decalactone and [Delta]-dodecalactone when used separately or in combination in oleomargarine are used at levels not to exceed 10 parts per million and 20 parts per million, respectively, in accordance with 166.110 of this chapter.

(d) BHA (butylated hydroxyanisole) may be used as an antioxidant in flavoring substances whereby the additive does not exceed 0.5 percent of the essential (volatile) oil content of the flavoring substance.

(e) The following flavoring substances shall not be used as a flavor in food.

Benzophenone; diphenylketone.
Ethyl acrylate.
Eugenyl methyl ether; 4-allylveratrole; methyl eugenol.
Myrcene; 7-methyl-3-methylene-1,6-octadiene.
Pulegone; *p*- menth-4(8)-en-3-one.
Pyridine.
Trans,*trans*-2,4-hexadienal.
Styrene.