In addition to the 19 constituents FDA proposes to add to the list of Harmful and Potentially Harmful Constituents, FDA should also add compounds that may be carcinogenic or cause pulmonary or cardiovascular harms when inhaled, especially oils and chemicals and chemical classes found in e-cigarette flavorants, and FDA should use as additional criteria California's Proposition 65 list of carcinogens and reproductive toxicants and the California Air Resources Board's list of Toxicant Air Contaminants

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FDA is proposing to add the following 19 toxicants that may be found in tobacco products, including electronic cigarettes, to the list of HPHCs: acetic acid, acetoin, (also known as 3-hydroxy-2-butanon3), acetyl propionyl (also known as 2,3-pentanedione), benzyl acetate, butyraldehyde, diacetyl, diethylene glycol, ethyl acetate, ethyl acetoacetate, ethylene glycol, furfural, glycerol, glycidol, isoamyl acetate, isobutyl acetate, methyl acetate, n-butanol, propionic acid, propylene glycol. (These constituents are shown in Table 1 of FDA's Notice and Request for Comments.) ***We support adding these 19 toxicants to the HPHC list.***

The proposed list, however, omits several important toxicants delivered by new products, notably e-cigarettes and heated tobacco products. In addition to the 19 toxicants FDA proposed, the list should be expanded to include other important toxicants and chemical classes delivered by these products. It its especially important for FDA to update the HPHC list to take into account the ingredients, additives, and smoke and aerosol constituents in e-cigarettes and other newly deemed tobacco products (including cigars, hookah, and heated tobacco products such as IQOS) that will likely be included in PMTAs filed in the coming months.

In particular, FDA's failure to consider 56 of the chemicals reported by PMI[1] to be higher in IQOS emissions than in reference cigarette mainstream smoke that were not included in the current list of 93 HPHCs may have contributed to FDA's inappropriate decision to approve the IQOS PMTA.[2]

FDA first established the HPHC list in April 2012, and the list currently contains 93 HPHCs.[3] ***FDA's proposal appropriately recognizes that the HPHC list that was established in 2012 does not reflect the current range of tobacco products now subject to the Agency's***

[1] St.Helen G, Jacob III P, Nardone N*, et al*., IQOS: examination of Philip Morris International's claim of reduced exposure. *Tobacco Control* 2018;**27:**s30-s36.
[2] https://tobacco.ucsf.edu/fda-sets-exceptionally-low-bar-when-authorizing-iqos-new-tobacco-products
[3] FDA, Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List (April 2012). Available at: https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list

tobacco product authorities or their health effects, including electronic cigarettes, heated tobacco products, and their associated components and parts.

The 2012 HPHC list is heavily weighted towards carcinogens; however, the major health effects identified for e-cigarettes include cardiovascular[4] and pulmonary impacts.[5] Even before the recent reports of serious lung ailments and deaths in teens and young adults that may be associated with cannabis or nicotine e-cigarette vaping,[6] evidence mounted that e-cigarettes may have considerable cardiopulmonary effects. An August 2019 peer-reviewed paper[7] concluded that using e-cigarettes induces nicotine-dependent protease release from resident pulmonary immune cells. Thus, chronic e-cigarette use disrupts the protease-antiprotease balance by increasing proteolysis in the lung, which may place e-cigarette users at risk of developing chronic lung disease. These data raise significant concern about how dangerous e-cigarettes are.

Also, the list does not include ultrafine particles or chemicals in flavoring agents used in e-liquids and flavored e-cigarettes which affect cardiovascular[8] and pulmonary systems.[9] The

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[4] Caporale A, Langham MC, Guo W, et al., Acute Effects of Electronic Cigarette Aerosol Inhalation on Vascular Function Detected at Quantitative MRI. Radiology 2019; 00:1–10. https://doi.org/10.1148/radiol.2019190562;
Bhatta DN, Glantz SA Electronic Cigarette Use and Myocardial Infarction Among Adults in the US Population Assessment of Tobacco and Health.. J Am Heart Assoc. 2019 Jun 18;8(12):e012317. doi: 10.1161/JAHA.119.012317. Epub 2019 Jun 5;
Fetterman JL, Weisbrod RM, Feng B, et al. Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction. Arterioscler Thromb Vasc Biol. 2018;38(7):1607–1615. doi:10.1161/ATVBAHA.118.311156

[5] Madison MC, Landers CT, Gu BH, et al., Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2019 Sep 4. pii: 128531. doi: 10.1172/JCI128531. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31483291;
Ghosh A, Coakley RD, Ghio AJ, et al., Chronic E-Cigarette Use Increases Neutrophil Elastase and Matrix Metalloprotease Levels in the Lung. Am J Respir Crit Care Med. 2019 Aug 7. doi: 10.1164/rccm.201903-0615OC. [Epub ahead of print];

[6] Layden JE, Ghinai I, Pray I, et al., Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Preliminary Report. N Engl J Med. 2019 Sep 6. doi: 10.1056/NEJMoa1911614. [Epub ahead of print];
CDC, Outbreak of Lung Disease Associated with E-Cigarette Use, or Vaping. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html;
FDA, Statement on federal and state collaboration to investigate respiratory illnesses reported after use of e-cigarette products. https://www.fda.gov/news-events/press-announcements/statement-federal-and-state-collaboration-investigate-respiratory-illnesses-reported-after-use-e

[7] Ghosh A, Coakley RD, Ghio AJ, et al., Chronic E-Cigarette Use Increases Neutrophil Elastase and Matrix Metalloprotease Levels in the Lung. Am J Respir Crit Care Med. 2019 Aug 7. doi: 10.1164/rccm.201903-0615OC. [Epub ahead of print]

[8] Fetterman JL, Weisbrod RM, Feng B, et al. Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction. Arterioscler Thromb Vasc Biol. 2018;38(7):1607–1615. doi:10.1161/ATVBAHA.118.311156

[9] Madison MC, Landers CT, Gu BH, et al., Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2019 Sep 4. pii: 128531. doi: 10.1172/JCI128531. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31483291;
Ghosh A, Coakley RD, Ghio AJ, et al., Chronic E-Cigarette Use Increases Neutrophil Elastase and Matrix Metalloprotease Levels in the Lung. Am J Respir Crit Care Med. 2019 Aug 7. doi: 10.1164/rccm.201903-0615OC. [Epub ahead of print];

carcinogen pulegone, found in mint- and menthol-flavored e-cigarettes and smokeless tobacco,[10] may have health risks when inhaled.

Updating the HPHC list to consider effects beyond cancer is especially important in light of the July 2019 federal court order[11] requiring e-cigarette manufacturers to submit premarket tobacco product applications (PMTAs) by May 2020. In determining whether new tobacco products will obtain marketing authorization, applicants are required to submit a "full statement of the components, ingredients, additives, and properties, and of the principle or principles of operation" of the new product.[12] The Guidance for PMTAs provides, "For each new tobacco product, you should report the levels of harmful and potentially harmful constituents (HPHC), including smoke constituents, as appropriate to the product."[13] For new tobacco products that are smoke (e.g., cigarettes), quantitative levels should be determined in smoke generated using both the ISO and Canadian Intense smoking regimens. If an alternative to these testing methods is used, you should provide the basis for your selection of the alternative method." In its consideration of the potentially thousands of PMTAs that will be submitted within 7 months, FDA will need to analyze whether the ingredients, including flavors, additives, and smoke and aerosol constituents, are included on the list of HPHCs, and what effect they have on the health risks of that product.

Compounds that may be safe to ingest are not necessarily safe to inhale. The literature shows that some flavorants and other additives become lung irritants and potentially dangerous when inhaled, and compounds that may be safe when isolated can become harmful when they interact with other constituents. Several constituents of e-cigarettes may have cardiovascular and pulmonary as well as carcinogenic effects when they are heated and inhaled.

1. We support FDA's proposed addition of glycidol and ethylene glycol to the HPHC list applying the criteria that were applied for the original list

a. We support FDA's addition of glycidol to the list of HPHCs

FDA has tentatively concluded that in revising the HPHC established list, the agency should continue to apply the criteria that were originally applied when determining whether a constituent should be put on the list. Following a review of the data concerning degradation of glycerol when heated, and observing that glycidol can form and appear in heated e-cigarette aerosol, FDA has applied the original criteria and tentatively concluded that glycidol should be included on the HPHC list. FDA notes that the International Agency for Research on Cancer (IARC) has identified glycidol as a probable carcinogen.

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[10] Jabba SV, Jordt SE, Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. 2019 Sep 16. doi: 10.1001/jamainternmed.2019.3649. [Epub ahead of print]

[11] *Am. Acad. of Pediatrics v. Food & Drug Admin.*, Case No.: PWG-18-883 (D. Md. Jul. 12, 2019) Available at: https://casetext.com/case/am-acad-of-pediatrics-v-food-drug-admin-1

[12] Family Smoking Prevention and Tobacco Control Act § 910(b)(1)(B), Pub. L. No. 111-31, 123 Stat. 1776 (2009).

[13] FDA, Applications for Premarket Review of New Tobacco Products: Guidance for Industry, Draft Guidance, p. 17 (September 2011).

We support FDA's application of IARC criteria, and support the inclusion of glycidol on the HPHC list as a probable carcinogen. That said, as we discuss elsewhere in this comment, whether a chemical is a probable carcinogen should be one of several criteria FDA uses in determining whether to add a chemical to the HPHC list, and should not be the exclusive criterion.

b. We support FDA's addition of ethylene glycol to the list of HPHCs

FDA has tentatively concluded that ethylene glycol should also be included on the HPHC list, noting that the California Environmental Protection Agency (Cal EPA) identified ethylene glycol (ingested) as a reproductive toxicant based on its developmental toxicity.

We support FDA's application of Cal EPA criteria, and agree that certain products identified by Cal EPA as reproductive toxicants should be added to the HPHC list. That said, as we discuss elsewhere in this comment, FDA must not only consider whether a product is toxic when *ingested,* but also must consider whether a product is toxic when *inhaled*, whether or not it is toxic when ingested.

2. FDA should also consider constituents identified by the National Institute for Occupational Safety and Health (NIOSH) as having adverse respiratory effects as an additional criterion for determining whether a constituent should be added to the HPHC list, and should include 17 additional constituents that meet this criterion

We agree with FDA's proposal to use constituents identified by the National Institute for Occupational Safety and Health (NIOSH) as having adverse respiratory effects as an additional criterion for determining whether a constituent should be added to the HPHC list. We support FDA's proposal to add to the list 17 additional constituents that meet this criterion (acetic acid, acetoin, acetyl propionyl, benzyl acetate, butyraldehyde, diacetyl, ethyl acetate, ethyl acetoacetate, ethylene glycol (which also meets one of the criteria that were originally applied), furfural, glycerol, isoamyl acetate, isobutyl acetate, methyl acetate, n-butanol, propionic acid, and propylene glycol). FDA already considers whether NIOSH has identified a constituent as a potential occupational carcinogen in determining whether that constituent should be included on the HPHC list. ***But whether a constituent has adverse respiratory effects may be even more significant than its carcinogenic effects when considering the constituents in e-cigarettes and e-liquids that will be inhaled.***

a. We support FDA's addition of propylene glycol and glycerol to the HPHC list

A large contributor to the exploding appeal of e-cigarettes among both adults and adolescents is the effective delivery of nicotine in the form of an aerosol composed of the vehicle solvents propylene glycol (PG) and glycerol. These solvents are used to generate the aerosol without tobacco combustion. While FDA uses the chemical term "glycerol" in its list of 19 proposed additions to the HPHC list, this e-cigarette ingredient is also frequently called "glycerin" or "vegetable glycerin" and is abbreviated as "VG," and these terms are used

interchangeably. We will use the term "VG" in these comments to refer to glycerol, glycerin, and/or vegetable glycerin because much of the scientific literature uses "VG," consumers see the term "VG" because the PG/VG ratio is included in many descriptions of e-liquids currently on the market, and FDA uses the term "VG" in its proposed rule on Premarket Tobacco Product Applications (PMTAs).[14]

Short-term occupational exposure to PG causes irritation of the airways, likely by activation of the receptors TRRPV1 and TRPA1, which are known to promote inflammation linked to asthma development.[15] Consistent with this concept, Dow Chemical Company's Material Safety Data Sheet[16] for PG states that "At room temperature, exposure to vapor is minimal due to low volatility. ***Mist*** may cause irritation of upper respiratory tract..." (emphasis added; "mist" is a synonym for aerosol). PG/VG also causes increased expression of inflammatory mucous proteins such as MUC5AC in mice, an effect verified in users of e-cigarettes.[17]

A September 2019 peer-reviewed study[18] shows many ways in which exposure to PG and VG from e-cigarettes disrupts normal lung function. In the study, researchers exposed mice to e-cigarette aerosol without and with nicotine and found that the aerosol altered the lipid (fat) balance in the lungs in ways that depressed the ability of the lung macrophages to fight infections and disrupted normal product of surfactants (chemicals in the lungs that help keep the air-sacs from collapsing). The authors conclude that chronic e-cigarette aerosol aberrantly alters the physiology of lung epithelial cells and resident immune cells and promotes poor response to infectious challenge. ***Notably, they found that alterations in lipid homeostasis and immune impairment are independent of nicotine, thereby warranting more extensive investigations of the PG/VG and other chemicals used in e-cigarettes.***

Exogenous lipoid pneumonia due to exposure to glycerin-based oils in e-cigarettes was reported as early as April 2012.[19] VG in e-liquids has been tied to lung damage and has been

[14] FDA, Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed rule, § 1114.7(c)(3)(iii), Docket No. FDA-2019-N-2854. Available at: https://www.federalregister.gov/documents/2019/09/25/2019-20315/premarket-tobacco-product-applications-and-recordkeeping-requirements

[15] Wieslander G, Norbäck D, Lindgren T, Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occupational and Environmental Medicine* 2001;**58:**649-655; Niedermirtl, F., Eberhardt, M., Namer, B., Leffler, A., Nau, C., Reeh, P. W., & Kistner, K. (2018). Etomidate and propylene glycol activate nociceptive TRP ion channels. *Molecular Pain*. https://doi.org/10.1177/1744806918811699;
Caceres AI, Brackmann M, Elia MD, et al. A sensory neuronal ion channel essential for airway inflammation and hyperreactivity in asthma. Proc Natl Acad Sci USA 2009; 106: 9099–9104.

[16] The Dow Chemical Company, Safety Data Sheet, Propylene Glycol USP/EP, 03/25/13.

[17] Ghosh A, Coakley RC, Mascenik T, Rowell TR, Davis ES, Rogers K, et al. Chronic e-cigarette exposure alters the human bronchial epithelial proteome. *Am J Respir Crit Care Med*. 2018;198:67–76.

[18] Madison MC, Landers CT, Gu BH, et al., Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. J Clin Invest. 2019 Sep 4. pii: 128531. doi: 10.1172/JCI128531. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31483291

[19] McCauley L, Markin C, Hosmer D, An unexpected consequence of electronic cigarette use. Chest. 2012 Apr;141(4):1110-1113. doi: 10.1378/chest.11-1334

shown to form many toxic compounds when heated, including those on FDA's list of HPHCs, such as formaldehyde, acetaldehyde, and acrolein.[20]

Because of these harms, PG and VG should be added to the HPHC list.

In its proposed rule for PMTAs,[21] FDA appropriately requires applicants to specify the PG/VG ratio in e-liquids and e-cigarettes to determine whether permitting the marketing of the product would be appropriate for the protection of the public health. Most of the evidence of potential harm reported in the scientific literature has involved both of these compounds, and we are aware of no studies that allow proportioning health risk to the relative amount of one of these compounds as a proportion of another.[22] Nevertheless, the relative concentration of each humectant in the e-liquid influences the type and amount of thermal degradation products emitted, which may translate to differential health risk. For example, one study found that PG-based e-liquid generated higher levels of formaldehyde and acetaldehyde than VG-based e-liquid by a factor of 2 and 12, respectively.[23]

3. We support FDA's addition of diethylene glycol to the HPHC list

FDA proposes to add diethylene glycol (DEG) to the HPHC because of concerns that a product that contains either VG or PG also could be contaminated by DEG, and the acute health consequences from exposure to DEG-contaminated products may be serious and irreversible. We agree.

4. FDA should add additional chemicals or chemical compounds to the existing HPHC list because they are harmful or potentially harmful to consumers when they are heated and inhaled in e-cigarettes, heated tobacco products, and other tobacco products.

The existing HPHC list focuses primarily on harmful constituents that are produced from combustible cigarettes. However, since that list was established in 2012, products (including but not limited to e-cigarettes and IQOS) that electronically heat tobacco, nicotine, flavorants, and/or other additives are, or soon will be, marketed in the United States.

a. Pulegone should be added to the HPHC list

[20] Wang P, Chen W, Liao J, Matsuo T, Ito K, et al. (2017) A Device-Independent Evaluation of Carbonyl Emissions from Heated Electronic Cigarette Solvents. PLOS ONE 12(1): e0169811. https://doi.org/10.1371/journal.pone.0169811

[21] FDA, Premarket Tobacco Product Applications and Recordkeeping Requirements, Proposed rule, § 1114.7(c)(3)(iii), Docket No. FDA-2019-N-2854. Available at: https://www.federalregister.gov/documents/2019/09/25/2019-20315/premarket-tobacco-product-applications-and-recordkeeping-requirements

[22] Wang P, Chen W, Liao J, Matsuo T, Ito K, et al. (2017) A Device-Independent Evaluation of Carbonyl Emissions from Heated Electronic Cigarette Solvents. PLOS ONE 12(1): e0169811. https://doi.org/10.1371/journal.pone.0169811

[23] Son Y. Estimating the human health risks associated with exposures to harmful constituents emitted from electronic cigarettes (Doctoral dissertation, Rutgers University-School of Graduate Studies).

Pulegone, a constituent of oil extracts prepared from mint plants, is a carcinogen that causes hepatic carcinomas, pulmonary metaplasia, and other neoplasms in rodents, and can also cause liver and kidney failure. Although the FDA banned synthetic pulegone as a food additive in 2018 and the chemical is banned in the European Union and in the state of California, substantial amounts of pulegone have been detected in mint- and menthol-flavored e-cigarette liquids and smokeless tobacco products. A September 2019 analysis[24] measured daily pulegone exposure from e-cigarettes and smokeless tobacco at higher levels compared with exposure from menthol cigarettes and compared the risk associated with pulegone content in combustible menthol cigarettes to the pulegone content in mint- and menthol-flavored e-cigarettes and smokeless tobacco.

The margin of exposure (MOE) is the measure used by the FDA and other regulatory agencies for cancer risk assessment of food additives, and cancer risk is inversely proportional to the MOE, with values of 10,000 or below requiring mitigation strategies. This study found that the MOE for all the products that were analyzed are below the accepted MOE threshold of 10,000 for carcinogens. This suggests that users of mint- and menthol-flavored e-cigarettes and smokeless tobacco are exposed to pulegone levels higher than the FDA considers unacceptable for intake of synthetic pulegone in food, and higher than in smokers of combustible menthol cigarettes. (March 2019 study[25] found that mint-, menthol-, and cucumber-flavored Juul pods, not studied in the Jabba/Jordt analysis, also contain pulegone.

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

b. Vitamin E acetate should be added to the HPHC list

On September 6. 2019 the New England Journal of Medicine (NEJM) published a report[26] describing 53 cases of severe pulmonary disease associated with the use of vaping products among generally young, healthy persons. As of September 27, 2019, at least 805 cases of serious lung illness associated with the use of vaping products had been reported to the CDC[27] from 46 states and 1 U.S. territory, and 12 deaths have been confirmed in 10 states.

While no single product is linked to all cases of lung disease, vitamin E acetate (tocopheryl acetate) may be responsible for some of the reported cases of severe pulmonary disease because it is used in cannabis (THC) oil vaporizers. The extent to which vitamin E

[24] Jabba SV, Jordt SE, Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. 2019 Sep 16. doi: 10.1001/jamainternmed.2019.3649. [Epub ahead of print]

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

[26] Layden JE, Ghinai I, Pray I, et al., Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Preliminary Report. N Engl J Med. 2019 Sep 6. doi: 10.1056/NEJMoa1911614. [Epub ahead of print]

[27] CDC, Outbreak of Lung Disease Associated with E-Cigarette Use, or Vaping. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html

acetate has been used in e-cigarettes is not known but cannot be ruled out due to a lack of oversight of e-cigarette manufacturing and the ease of product manipulation by retailers and users. Vitamin E acetate is not known to be harmful when ingested as a vitamin supplement or when applied to the skin, but data on its inhalation effects suggest that its oil-like properties could be associated with the observed pulmonary symptoms.[28] Exogenous lipoid pneumonia can occur when an oil is inhaled. Once inhaled into the lungs, the oil can cause an inflammatory reaction, and the severity of the reaction can depend on the length of exposure. Severe inflammation can permanently damage the lungs. Lipid-laden macrophages and acute lung injury associated with e-cigarette inhalation has been reported previously.[29]

The NEJM report states:

> E-cigarette liquids and aerosols have been shown to contain a variety of chemical constituents that may have adverse health effects. [fn] Major declared constituents in nicotine-based e-cigarettes include propylene glycol and glycerin, [fn] in addition to nicotine. Identified contaminants include polycyclic aromatic hydrocarbons, nitrosamines, volatile organic chemicals, and inorganic chemicals such as toxic metals. [fn] Endotoxins and flavoring compounds such as diacetyl and 2,3-pentanedione have also been detected. [fn] The health risks of some constituents remain poorly characterized, and toxicologic assessment of these substances is an active area of ongoing research. [fn] In addition to nicotine, e-cigarette devices can be used to deliver a variety of other recreational drugs, including THC-based oils. [fn]

Until more data are available and analyzed, FDA should adopt the precautionary principle and add to the HPHC list vitamin E acetate and other "oils" (fatty acids).

5. Flavorants and other additives in e-cigarettes, heated tobacco products, and other deemed tobacco products become lung irritants when inhaled, so FDA must consider the chemical reaction that occurs when these constituents are heated (even if not combusted) and inhaled.

When considering flavorants and other additives in e-cigarettes, heated tobacco products, and other products that produce inhaled aerosols, FDA must not rely on previously established designations that these constituents are "generally recognized as safe" (GRAS) for ingestion. ***Inhalation is a fundamentally different exposure mode than ingestion, so the fact that a substance is GRAS for ingestion provides no useful information regarding safety for inhalation.***

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[28] Sun, LH, Contaminant found in marijuana vaping products linked to deadly lung illnesses, tests show. https://www.washingtonpost.com/health/2019/09/05/contaminant-found-vaping-products-linked-deadly-lung-illnesses-state-federal-labs-show/

[29] Masayuki I, Kazutetsu A, Yoriko H, et al., Lung injury associated with electronic cigarettes inhalation diagnosed by transbronchial lung biopsy. Respirology Case Reports, 6 (1), 2018, e00282, doi: 10.1002/rcr2.282

Erythropel et al.'s October 2018 study[30] found flavor aldehyde PG acetals in commercial e-liquids, and concluded that e-liquids are potentially reactive chemical systems in which new compounds can form after mixing of constituents and during story, and these can have unexpected toxicological effects. Erythropel et al.'s 2019 study[31] reported the presence of flavor aldehyde VG acetals in e-liquids and aerosols, and found that the compounds present in some Juul e-liquids (e.g., crème brulee) are delivered efficiently to the aerosol when heated, exposing users to the PG and VG acetals of vanillin. Appreciable amounts of acetals were present in the aerosol which, if inhaled, may cause irritation and contribute to inflammatory responses. This study demonstrates that e-cigarette liquids can be chemically unstable, with reactions occurring between flavorant and solvent components immediately after mixing at room temperature. The resulting compounds have toxicological properties that differ from either the flavorants or solvent components. ***These findings suggest that the reporting of manufacturing ingredients of e-liquids (including the reporting of HPHCs) is not alone sufficient for a safety assessment. Rather, to effectively analyze the risks, FDA should require companies to establish an analytical workflow to detect newly formed compounds in e-liquids and their potential toxicological effects.***[31]

Omaiye et al.[32] studied the flavor chemical and nicotine concentrations in 8 currently marketed Juul e-cigarette pods to evaluate the cytotoxicity and potential health impacts. They identified 59 flavor chemicals in Juul pod fluids, and found that all pod fluids were cytotoxic at a 10% dilution, and most aerosols were cytotoxic at concentrations between 0.2 and 1.8%. The study demonstrated that not only are the Juul flavor pods attractive to youth, but the concentrations of nicotine and some flavor chemicals (e.g., ethyl maltol) are high enough to be cytotoxic in acute *in vitro* assays, suggesting that Juul products could lead to adverse health effects with chronic use.

As described above, Jordt and Jabba found[33] that mint- and menthol-flavored e-cigarettes contain extremely high levels of pulegon.

Further, a study by Khlystov and colleagues suggests that flavors are major contributors to emissions of toxic aldehydes from e-cigarettes.[34]

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[30] Erythropel HC, Jabba SV, deWinter TM, et al., Formation of flavorant–propylene Glycol Adducts With Novel Toxicological Properties in Chemically Unstable E-Cigarette Liquids, *Nicotine & Tobacco Research*, Volume 21, Issue 9, September 2019, Pages 1248–1258, https://doi.org/10.1093/ntr/nty192

[31] Erythropel HC, Davis LM, deWinter TM, et al., Flavorant-Solvent Reaction Products and Menthol in JUUL E-Cigarettes and Aerosol. Am J Prev Med. 2019 Sep;57(3):425-427. doi: 10.1016/j.amepre.2019.04.004. Epub 2019 Jul 27.

[32] Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations. *Chem Res Toxicol.* 2019;32:1058-1069.

[33] Jabba SV, Jordt SE, Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. 2019 Sep 16. doi: 10.1001/jamainternmed.2019.3649. [Epub ahead of print]

[34] Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. Environ Sci Technol. 2016;50(23):13080-5.

These findings build on a 2016 study[35] that investigated the cellular effects of exposure to e-cigarette aerosol and the impact of various product characteristics on potential inhalation toxicity of e-cigarette products. The researchers found that exposure to e-cigarette aerosol resulted in decreased metabolic activity and cell viability, and flavors in e-liquids can have an acute cytotoxic effect on respiratory cells. In this study, menthol, coffee, and strawberry flavors had a significant impact on overall cytotoxicity of e-cigarette products. (although the study did not look at which of the flavoring compounds caused this cytotoxicity and release of inflammatory mediators, and only one e-liquid product was tested for each flavor name. The study also confirmed that increasing the device power by increasing battery output voltage resulted in significantly higher overall toxicity of e-cigarette aerosol.

Earlier studies had already found that inhalation of complex mixtures like flavored e-cigarette aerosols can cause a wide range of adverse health effects, ranging from simple irritation to systemic diseases.[36] Cinnamon flavorings in refill fluids were found to be linked to cytotoxicity, which could adversely affect e-cigarette users.[37]

Clapp et al showed that inhalation of cinnamaldehyde in flavored e-cigarette liquids may increase the risk of respiratory infections in e-cigarette users.[38] Gerloff et al showed that flavorings such as acetoin (butter), diacetyl, pentanedione, maltol (malt), ortho-vanillin (vanilla), coumarin, and cinnamaldehyde in some flavored e-cigarette liquids and aerosols can cause significant loss of epithelial barrier function and proinflammatory response in lung cells.[39] Muthumalage et al found that commonly used e-cigarette flavoring chemicals, including diacetyl, cinnamaldehyde, acetoin, pentanedione, o-vanillin, maltol and coumarin, can trigger an inflammatory response in monocytes and increased oxidative stress, and mixing a variety of flavors results in greater cytotoxicity and oxidative stress and may be more harmful to users, providing insights into potential pulmonary toxicity and tissue damage in e-cigarette users.[40] Park et al found that two widely used e-cigarette flavoring chemicals, diacetyl (often used in butter flavors) and its substitute 2,3-pentanedione, impair the cilia function in airway epithelium and likely contribute to the adverse effects of e-cigarettes in the lung.[41]

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[35] Leigh NJ, Lawton RI, Hershberger PA, Goniewicz ML. Flavourings significantly affect inhalation toxicity of aerosol generated from electronic nicotine delivery systems (ENDS). Tob Control. 2016;25(Suppl 2):ii81–ii87. doi:10.1136/tobaccocontrol-2016-053205

[36] Hayes A, Bakand S. Inhalation Toxicology. In: Luch A, editor. Molecular, Clinical and Environmental Toxicology. Basel, Switzerland: Birkhäuser; 2010. pp. 461–88

[37] Behar R, Davis B, Wang Y, et al. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. Toxicol In Vitro. 2014;28:198–208. doi: 10.1016/j.tiv.2013.10.006

[38] Clapp PW, Lavrich KS, van Heusden CA, et al., Cinnamaldehyde in flavored e-cigarette liquids temporarily suppresses bronchial epithelial cell ciliary motility by dysregulation of mitochondrial function. Am J Physiol Lung Cell Mol Physiol 2019 Mar 1;316(3):L470-L486. doi: 10.1152/ajplung.00304.2018. Epub 2019 Jan 3.

[39] Gerloff J, Sundar IK, Freter R et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography-mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. Appl Vitro Toxicol 2017; 3(1): 28–40

[40] Muthumalage T., Prinz M., Ansah K.O., Gerloff J., Sundar I.K., Rahman I. Inflammatory and Oxidative Responses Induced by Exposure to Commonly Used e-Cigarette Flavoring Chemicals and Flavored e-Liquids without Nicotine. Front. Physiol. 2017;8:1130. doi: 10.3389/fphys.2017.01130.

[41] Park HR, O'Sullivan M, Vallarino J, Shumyatcher M, Himes BE, Park JA, et al. Transcriptomic response of primary human airway epithelial cells to flavoring chemicals in electronic cigarettes. Sci Rep. 2019;9(1):1400. doi: 10.1038/s41598-018-37913-9

a. Flavored e-liquids exacerbate vascular endothelial dysfunction, which often precedes cardiovascular diseases

September 2019 study[42] investigated the effects of flavored e-liquids on endothelial health and endothelial cell-dependent macrophage activation. The study found that acute exposure of human-induced pluripotent stem cell-derived endothelial cells to e-liquids containing several popular flavors, or to serum from e-cigarette users, leads to changes in cellular properties indicative of endothelial dysfunction, which often precedes cardiovascular diseases. The data revealed a range of cytotoxicity of the e-liquids, with the cinnamon-flavored e-liquid being most toxic and leading to significantly decreased cell viability, increased reactive oxygen species (ROS) levels, caspase 3/7 activity, and low-density lipoprotein uptake, activation of oxidative stress-related pathway, which are all consistent with endothelial dysfunction. The ability of endothelial cells to form tubular networks, and cell migration into cell-free regions, were also impaired. Conditioned media from the endothelial cells after exposure to e-liquid induced macrophage polarization into a pro-inflammatory state, leading to the production of interleukin-1β and -6, and an increase in ROS. Exposure of endothelial cells to serum of e-cigarette users also increased ROS levels in the cells and impaired their pro-angiogenic properties. Inflammatory cytokine levels in the serum of e-cigarette users were increased. Other studies have also shown various kinds of cytotoxicity *in vitro* for common flavors.[43, 44]

In addition to continuing to apply the criteria that were originally applied when determining whether a constituent should be put on the 2012 list of HPHCs, which largely considered whether a chemical is carcinogenic, FDA should evaluate whether a chemical exacerbates endothelial dysfunction in particular, and in general whether exposure to a chemical may have cardiovascular effects.

In addition to continuing to apply the criteria that were originally applied when determining whether a constituent should be put on the 2012 list of HPHCs, FDA should also evaluate whether chemicals, especially those that are used in e-cigarette flavorings, are potentially harmful when inhaled, regardless of whether they are GRAS for ingestion.

6. Although menthol has not itself been shown to be toxic, FDA should include it on the HPHC list because of its interaction with nicotine and tobacco carcinogens

In addition to menthol-flavored conventional cigarettes (i.e., cigarettes marketed with

[42] Lee, W., Ong, S., Zhou, Y., Tian, L., Bae, H., Baker, N., et al. (2019). Modeling Cardiovascular Risks of E-Cigarettes With Human-Induced Pluripotent Stem Cell-Derived Endothelial Cells. Journal of the American College of Cardiology, 73(21), 2722-2737. http://dx.doi.org/10.1016/j.jacc.2019.03.476 Retrieved from https://escholarship.org/uc/item/0th760sk

[43] Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations. *Chem Res Toxicol.* 2019;32:1058-1069.

[44] Fetterman JL, Weisbrod RM, Feng B, Bastin R, Tuttle ST, Holbrook M, Baker G, Robertson RM, Conklin DJ, Bhatnagar A, Hamburg NM. Flavorings in Tobacco Products Induce Endothelial Cell Dysfunction. *Arterioscler Thromb Vasc Biol.* 2018;38:1607-1615.

"menthol" as a characterizing flavor, such as Newport or Kool), most cigarettes, even those that are not labeled menthol as a characterizing flavor, contain menthol as an ingredient. ***Likewise, e-cigarette liquids and other tobacco products include menthol as an ingredient, even if they are not sold as "menthol-flavored."***

In 2011 the FDA Tobacco Products Scientific Advisory Committee (TPSAC) issued a report concluding that "removal of menthol cigarettes from the marketplace would benefit public health in the United States."[45] FDA independently undertook a thorough review of the available science concerning menthol in cigarettes and issued its own report in 2013. Using a "weight of scientific evidence" approach, FDA's independent analysis found that: (1) menthol use is likely associated with increased smoking initiation by youth and young adults; (2) menthol in cigarettes is likely associated with greater addiction; (3) menthol smokers show greater signs of nicotine dependence and are less likely to successfully quit smoking; (4) menthol's cooling and anesthetic properties can reduce the harshness of cigarette smoke; and (5) menthol cigarettes are marketed as a smoother alternative to non-menthol cigarettes. Considering this combined evidence, FDA concluded that these findings "make it likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes."[46]

Although menthol is not a direct cause of disease, menthol has an important indirect effect on disease risk because it interferes with the clearance of tobacco-specific carcinogens. In particular, menthol biologically interacts with nicotine and tobacco carcinogens, and increases exposure to harmful carcinogens.[47] Tissues in the body that are directly exposed to tobacco are especially vulnerable to developing primary tobacco-related cancer tumors.[48] These tissues have difficulty with the biological clearance (removal) of tobacco carcinogens (e.g., NNAL), and ***the presence of menthol, even at low levels (below that needed to have menthol be a "characterizing flavor"), decreases the body's ability to detoxify tobacco carcinogens***.[49]

This situation may explain why "menthol cigarettes" (i.e., cigarettes for which menthol is a characterizing flavor) have not been associated with increased cancer incidents over "non-menthol cigarettes" (i.e., cigarettes for which menthol is not a "characterizing flavor"). The high levels of menthol in "menthol cigarettes" may be having effects on blocking clearance of carcinogens similar to the low levels of menthol in "non-menthol" cigarettes. Because the levels of menthol in both "menthol" and "non-menthol" cigarettes both reduce clearance of tobacco

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[45] FDA Tobacco Products Scientific Advisory Committee Menthol Cigarettes and Public Health: Review of the Scientific Evidence and Recommendations. March 23, 2011

[46] FDA Center for Tobacco Products, Preliminary Scientific Evaluation of the Possible Public Health Effects of Menthol Versus Nonmenthol Cigarettes. July 23, 2013.

[47] Benowitz, N. L.; Dains, K. M.; Dempsey, D.; Havel, C.; Wilson, M.; Jacob, P., 3rd, Urine menthol as a biomarker of mentholated cigarette smoking. *Cancer Epidemiol Biomarkers Prev* **2010,** *19* (12), 3013-9;
Hsu, P. C.; Lan, R. S.; Brasky, T. M.; Marian, C.; Cheema, A. K.; Ressom, H. W.; Loffredo, C. A.; Pickworth, W. B.; Shields, P. G., Menthol Smokers: Metabolomic Profiling and Smoking Behavior. *Cancer Epidemiol Biomarkers Prev* **2017,** *26* (1), 51-60;
Kramlinger, V. M.; von Weymarn, L. B.; Murphy, S. E., Inhibition and inactivation of cytochrome P450 2A6 and cytochrome P450 2A13 by menthofuran, beta-nicotyrine and menthol. *Chem Biol Interact* **2012,** *197* (2-3), 87-92.

[48] Kozlovich, S.; Chen, G.; Watson, C. J. W.; Lazarus, P., Prominent Stereoselectivity of NNAL Glucuronidation in Upper Aerodigestive Tract Tissues. *Chem Res Toxicol* **2019,** *32* (8), 1689-1698.

[49] Kozlovich, S.; Chen, G.; Watson, CJW.; Blot, WJ.; Lazarus, P., The Role of L- and D-menthol in the Glucuronidation and Detoxification of the Major Lung Carcinogen, NNAL. *Drug Metab Disop.* In press

carcinogens, comparing the effects of menthol and non-menthol cigarettes would not show any difference in risk, even though menthol is increasing carcinogen exposure in both classes of products. Specifically, the failure to find an association between menthol and cancer risk may be due to the fact that menthol's effects on carcinogen detoxification can occur at levels below that associated with menthol as a characterizing flavor.

Thus, menthol as an ingredient, even at levels below those needed to qualify menthol as a characterizing flavor, can increase cancer risk by slowing clearance of tobacco carcinogens from the body.

7. FDA should use the following additional criteria in deciding whether to add a constituent to the list of HPHCs:

a. FDA should include on the HPHC list constituents identified by the State of California known to be human carcinogens or reproductive toxins (Proposition 65 list) or a toxic air contaminant

The State of California maintains a list of chemicals known to cause cancer or reproductive toxicity known as the "Proposition 65 list."[50] (Appendix). Chemicals go through an extensive review process, including public notice and comment, so are thoroughly vetted.[51]

The Proposition 65 list includes chemicals identified by the World Health Organization International Agency for Research on Cancer (IARC) as causing cancer in humans or laboratory animals. It also includes chemicals identified by two California scientific committees, the Carcinogen Identification Committee and the Developmental and Reproductive Toxicant Identification Committee. It also includes chemicals identified by "authoritative bodies" (the US Environmental Protection Agency, US Food and Drug Administration (US FDA), National Institute for Occupational Safety and Health, the National Toxicology Program of the US Department of Health and Human Services, and IARC.)

The FDA should consider the California Proposition 65 list an authoritative body and include the full range of chemicals on the Proposition 65 list now and in the future as part of the updated FDA HPHC list.

b. FDA should include on the HPHC list constituents identified by the California Air Resources Board (CARB) as "Toxic Air Contaminants" under the Toxic Air Contaminant Identification and Control Act

The California Air Resources Board (CARB) has identified and regulated "Toxic Air Contaminants" under the Toxic Air Contaminant Identification and Control Act (AB 1807, Tanner 1983).[52] In selecting substances for review, the CARB must consider criteria relating to "the risk of harm to public health, amount or potential amount of emissions, manner of, and

[50] https://oehha.ca.gov/proposition-65/proposition-65-list
[51] https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list
[52] https://ww3.arb.ca.gov/toxics/background.htm

exposure to, usage of the substance in California, persistence in the atmosphere, and ambient concentrations in the community" [Health and Safety Code section 39666(f)]. The law establishes a two-step process of risk identification and risk management to address the potential health effects from air toxic substances and protect the public health of Californians. The first (identification) step is relevant for the FDA HPHC list.

The identification step begins with the CARB and the California Environmental Protection Agency Office of Environmental Health Hazard Assessment (OEHHA) determining if a substance should be formally identified as a toxic air contaminant (TAC) in California. During this process, the CARB and the OEHHA staff draft a report that serves as the basis for this determination. The CARB staff assesses the potential for human exposure to a substance and the OEHHA staff evaluates the health effects. A thorough public process assures accountability and public input through one. Staff conducts public workshops to allow for direct exchanges of information with interested constituencies, publishes the draft risk assessments, and widely distributes with a public notice requesting comments. The final risk assessment (identification) report includes a record of the public comments and how they were addressed. After the CARB and the OEHHA staff hold several comment periods and workshops, the report is then submitted to the independent, nine-member, Scientific Review Panel (SRP), who reviews the report for its scientific accuracy. After the SRP's approval, CARB staff prepare a hearing notice and draft regulation to formally identify the substance as a TAC. Based on the input from the public and the information gathered from the report, the Board decides whether to identify a substance as a TAC.

The current list of TACs[53] is

- Acetaldehyde
- Asbestos
- Benzene
- Benzo[a]pyrene
- 1,3-Butadiene
- Cadmium
- Carbon Tetrachloride
- Chlorinated Dioxins
- Chloroform
- Diesel Exhaust[a]
- Ethylene Dibromide
- Ethylene Dichloride
- Ethylene Oxide
- Formaldehyde
- Hexavalent Chromium
- Inorganic Arsenic
- Inorganic Lead[b]
- Methylene Chloride
- Methyl Tertiary Butyl Ether[c]

[53] https://oehha.ca.gov/air/general-info/toxic-air-contaminant-list-staff-reportsexecutive-summaries. This page also includes links to the executive summaries of the SRP-approved risk assessment documents.

- Naphthalene[d]
- Nickel
- Perchloroethylene
- Trichloroethylene
- Vinyl Chloride

These chemicals list should be included in the updated FDA HPHC list and the California TAC list should become an authoritative body that FDA relies on for furture additions to the HPHL list.

After a public process similar to that described for TACs, the SRP also approved a report identifying TACs that may disproportionately impact infants and children as required by California's Children's Environmental Health Protection Act (SB 25, Escutia; chaptered 1999). These compounds, listed in Table 1 (copied from Table 4 of the report *Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act*) should be highlighted in FDA's new HPHC list.[54]

Table 1. TACs that may disproportionately impact infants and children.

Toxic Air Contaminant	Endpoints of Most Concern	Major Reasons Why Chosen
Tier 1 TACs		
Acrolein	Respiratory Irritant	Exacerbation of asthma; modeling predictions indicate concentrations in urban air above cREL
Chlorinated dioxins and dibenzofurans (dioxins)	Developmental toxicity, immunotoxicity, endocrine disruption; thyroid effects	Widespread exposure; endocrine disruption, thyroid and immuno-toxicity at low body burden; young animals more susceptible than older animals
Lead and compounds	Developmental neurotoxicity/CNS effects	Children the most susceptible subpopulation due to developmental neurotoxicity.
Particulate Emissions from Diesel-fueled Engines (Diesel exhaust particulate matter)	Enhancement of allergic response; exacerbation of asthma; developmental effects, genotoxicity and lung cancer.	Enhancement of allergic response and implications for exacerbation and possible induction of asthma; Major source of ambient PAHs, PM10; exacerbation of asthma by PM10; PAH developmental toxicity and genotoxicity a concern.
Polycyclic Organic Matter (POM)	Developmental effects, genotoxicity and lung cancer	Animal studies indicate teratogenicity, and fetotoxicity; human studies indicate greater genotoxicity following in utero exposures.
Tier 2 TACs		
Arsenic and compounds (inorganic)	Carcinogenicity; potential neurotoxicity	Evidence of increased susceptibility to carcinogenicity early in life; possible neurotoxicity
Benzene	Hematopoietic effects, carcinogen	Widespread exposure; studies suggest possible increased risk of childhood leukemia in children of benzene-exposed workers.

[54] Office of Environmental Health Hazard Assessment California Environmental Protection Agency. Prioritization of Toxic Air Contaminants Under the Children's Environmental Health Protection Act. October, 2001. https://oehha.ca.gov/media/downloads/air/report/sb2520tac20prioritization.pdf. (Accessed 25 Sep 2019).

Carbon disulfide	Neurotoxic effects; possible developmental toxicity	Neurotoxicity a key toxicological endpoint for children; metabolism slow in neonate; lower lethal dose in neonatal mice.
Chlorine	Respiratory irritant	Exacerbation of asthma.
Formaldehyde	Respiratory irritant; carcinogen	Widespread exposure; cREL below urban ambient and indoor levels; exacerbation of asthma; indication that children more susceptible to lung function impacts.
Ethylene glycol ethers (EGEE, EGME, EGEEA, and EGMEA)	Developmental effects including teratogenicity	Teratogenic effects; large emissions of glycol ethers from stationary sources.
Manganese and compounds	Neurotoxicity	Neurotoxicity a key endpoint for infants and children.
Mercury and compounds	Developmental neurotoxicity	Children most susceptible subpopulation due to developmental neurotoxicity.
Methyl Bromide	Neurotoxicity	Infants and children are susceptible subpopulations for neurotoxicity.
Methylene chloride	Metabolized to carbon monoxide	Carbon monoxide has higher affinity for fetal hemoglobin; high emissions from stationary sources.
Polychlorinated Biphenyls (PCBs)	Developmental effects including neurotoxicity; thyroid effects; dioxin -like toxicity	Infants susceptible subpopulation for thyroid effects; infants and children for developmental neurotoxicity
Vinyl chloride	Carcinogenicity	Animal studies indicate much higher potency when exposure occurs in utero or perinatally than as mature animals.

8. The FDA should also consider *classes* of chemicals as well as specific chemicals

In addition to focusing on single chemicals that we know are toxic, FDA should also consider chemical classes. That is, inclusion unto the HPHC list should also be done based on the structure-activity relationships of chemicals for which their toxicity has not yet been specifically assessed but which are similar to known toxicants. Absent such an approach FDA will continuously be engaged in a wild-goose chase for the toxicity of the thousands of chemicals that are potentially added into e-cigarette flavors or heated-tobacco products.

For example, compared to a ref cigarette, IQOS had higher levels of 56 chemicals. These chemicals were most likely flavor additives and their derivatives. We do not know the toxicology of most of them. But as St. Helen et al observed in their IQOS paper that some of these chemicals "belong to chemical classes that are known to have significant toxicity, such as α,β-unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione), 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-), furans (eg, 2 (5H)-furanone) and epoxides (eg, anhydro linalool oxide).

The HPHC should, at a minimum, include:

- α,β-unsaturated carbonyl compounds
- 1,2-dicarbonyl compounds
- Furans
- Epoxides

It should also include "oils" (fatty acids), not just vitamin E acetate.

9. Conclusion

FDA will soon be required to review possibly hundreds of premarket tobacco product applications (PMTAs) that will be filed by the May 2020 deadline for filing PMTAs for newly deemed products including e-cigarettes, heated tobacco products, cigars, and hookah. Therefore, FDA must update the existing list of Harmful and Potentially Harmful Constituents (HPHCs) to take into account the ingredients, additives, and smoke and aerosol constituents that are likely to be found in these products.

We support FDA's 19 proposed additions to the HPHC list. In particular, we support the addition of the following chemicals that are frequently found in e-cigarette flavorants and additives:

- propylene glycol
- glycerol (also called "vegetable glycerin" or "glycerin")
- diacetyl
- pentanedione (or "2,3-pentanedione")

In addition to the 19 constituents FDA proposes to add to the HPHC list, FDA should also add other compounds that may be carcinogenic or cause pulmonary or cardiovascular harms when inhaled, especially chemicals found in e-cigarette flavorants. There is mounting scientific evidence suggesting that compounds that may be safe to ingest are not necessarily safe to inhale. The literature shows that some flavorants and other additives become lung irritants and potentially dangerous when inhaled, and compounds that may be safe when isolated can become harmful when they interact with other constituents. Several constituents of e-cigarettes may have cardiovascular, pulmonary, and carcinogenic effects when they are heated and inhaled.

In particular, FDA should add the following chemicals to the existing HPHC list:

- pulegone
- vitamin E acetate
- acetoin
- maltol
- ortho-vanillin (or "o-vanillin")
- coumarin
- cinnamaldehyde
- menthol
- α,β-unsaturated carbonyl compounds
- 1,2-dicarbonyl compounds
- furans
- epoxides

Finally, FDA should use additional criteria for additions to the HPHC list. FDA should

add constituents identified by the State of California on its Proposition 65 list of constituents known to be human carcinogens and constituents identified by the California Air Resources Board (CARB) as “Toxic Air Contaminants” under the Toxic Air Contaminant Identification and Control Act.

STATE OF CALIFORNIA
ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT
SAFE DRINKING WATER AND TOXIC ENFORCEMENT ACT OF 1986

CHEMICALS KNOWN TO THE STATE TO CAUSE CANCER OR REPRODUCTIVE TOXICITY
September 13, 2019

The Safe Drinking Water and Toxic Enforcement Act of 1986 requires that the Governor revise and republish at least once per year the list of chemicals known to the State to cause cancer or reproductive toxicity. The identification number indicated in the following list is the Chemical Abstracts Service (CAS) Registry Number. No CAS number is given when several substances are presented as a single listing. The date refers to the initial appearance of the chemical on the list. For easy reference, chemicals which are shown underlined are newly added. Chemicals or endpoints shown in strikeout were placed on the Proposition 65 list on the date noted, and have subsequently been removed.

Chemical	Type of Toxicity	CAS No.	Date Listed
A-alpha-C (2-Amino-9H-pyrido [2,3-b]indole)	Cancer	26148-68-5	January 1, 1990
Abiraterone acetate	developmental, female, male	154229-18-2	April 8, 2016
Acetaldehyde	cancer	75-07-0	April 1, 1988
Acetamide	cancer	60-35-5	January 1, 1990
Acetazolamide	developmental	59-66-5	August 20, 1999
Acetochlor	cancer	34256-82-1	January 1, 1989
Acetohydroxamic acid	developmental	546-88-3	April 1, 1990
2-Acetylaminofluorene	cancer	53-96-3	July 1, 1987
Acifluorfen sodium	cancer	62476-59-9	January 1, 1990
Acrylamide	cancer	79-06-1	January 1, 1990
Acrylamide	developmental, male	79-06-1	February 25, 2011
Acrylonitrile	cancer	107-13-1	July 1, 1987
Actinomycin D	cancer	50-76-0	October 1, 1989
Actinomycin D	developmental	50-76-0	October 1, 1992
AF-2;[2-(2-furyl)-3-(5-nitro-2-furyl)] acrylamide	cancer	3688-53-7	July 1, 1987
Aflatoxins	cancer	---	January 1, 1988
Alachlor	cancer	15972-60-8	January 1, 1989
Alcoholic beverages	cancer	---	April 29, 2011
Alcoholic beverages, when associated with alcohol abuse	cancer	---	July 1, 1988
Aldrin	cancer	309-00-2	July 1, 1988
All-trans retinoic acid	developmental	302-79-4	January 1, 1989
~~Allyl chloride,~~ Delisted October 29, 1999	~~cancer~~	~~107-05-1~~	~~January 1, 1990~~
Aloe Vera, non-decolorized whole leaf extract	cancer	---	December 4, 2015
Alprazolam	developmental	28981-97-7	July 1, 1990
Altretamine	developmental, male	645-05-6	August 20, 1999
Amantadine hydrochloride	developmental	665-66-7	February 27, 2001
Amikacin sulfate	developmental	39831-55-5	July 1, 1990
2-Aminoanthraquinone	cancer	117-79-3	October 1, 1989
p-Aminoazobenzene	cancer	60-09-3	January 1, 1990
o-Aminoazotoluene	cancer	97-56-3	July 1, 1987

Chemical	Type of Toxicity	CAS No.	Date Listed
4-Aminobiphenyl (4-amino-diphenyl)	cancer	92-67-1	February 27, 1987
2-Amino-4-chlorophenol	cancer	95-85-2	September 13, 2019
1-Amino-2,4-dibromo-anthraquinone	cancer	81-49-2	August 26, 1997
3-Amino-9-ethylcarbazole hydrochloride	cancer	6109-97-3	July 1, 1989
2-Aminofluorene	cancer	153-78-6	January 29, 1999
Aminoglutethimide	developmental	125-84-8	July 1, 1990
Aminoglycosides	developmental	---	October 1, 1992
1-Amino-2-methylanthraquinone	cancer	82-28-0	October 1, 1989
2-Amino-5-(5-nitro-2-furyl)-1,3,4-thiadiazole	cancer	712-68-5	July 1, 1987
4-Amino-2-nitrophenol	cancer	119-34-6	January 29, 1999
Aminopterin	developmental, female	54-62-6	July 1, 1987
Amiodarone hydrochloride	developmental, female, male	19774-82-4	August 26, 1997
Amitraz	developmental	33089-61-1	March 30, 1999
Amitrole	cancer	61-82-5	July 1, 1987
Amoxapine	developmental	14028-44-5	May 15, 1998
Amsacrine	cancer	51264-14-3	August 7, 2009
~~tert-Amyl methyl ether,~~ Delisted December 13, 2013	~~developmental~~	~~994-05-8~~	~~December 18, 2009~~
Anabolic steroids	female, male	---	April 1, 1990
Analgesic mixtures containing phenacetin	cancer	---	February 27, 1987
Androstenedione	cancer	63-05-8	May 3, 2011
Angiotensin converting enzyme (ACE) inhibitors	developmental	---	October 1, 1992
Aniline	cancer	62-53-3	January 1, 1990
Aniline hydrochloride	cancer	142-04-1	May 15, 1998
o-Anisidine	cancer	90-04-0	July 1, 1987
o-Anisidine hydrochloride	cancer	134-29-2	July 1, 1987
Anisindione	developmental	117-37-3	October 1, 1992
Anthraquinone	cancer	84-65-1	September 28, 2007
Antimony oxide (Antimony trioxide)	cancer	1309-64-4	October 1, 1990
Aramite	cancer	140-57-8	July 1, 1987
Areca nut	cancer	---	February 3, 2006
Aristolochic acids	cancer	---	July 9, 2004
Arsenic (inorganic arsenic compounds)	cancer	--	February 27, 1987
Arsenic (inorganic oxides)	developmental	---	May 1, 1997
Asbestos	cancer	1332-21-4	February 27, 1987
Aspirin (NOTE: It is especially important not to use aspirin during the last three months of pregnancy, unless specifically directed to do so by a physician because it may cause problems in the unborn child or complications during delivery.)	developmental, female	50-78-2	July 1, 1990
Atenolol	developmental	29122-68-7	August 26, 1997
Atrazine	developmental, female	1912-24-9	July 15, 2016
Auramine	cancer	492-80-8	July 1, 1987
Auranofin	developmental	34031-32-8	January 29, 1999
Avermectin B1 (Abamectin)	developmental	71751-41-2	December 3, 2010
Azacitidine	cancer	320-67-2	January 1, 1992
Azaserine	cancer	115-02-6	July 1, 1987

Chemical	Type of Toxicity	CAS No.	Date Listed
Azathioprine	cancer	446-86-6	February 27, 1987
Azathioprine	developmental	446-86-6	September 1, 1996
Azobenzene	cancer	103-33-3	January 1, 1990
Barbiturates	developmental	---	October 1, 1992
Beclomethasone dipropionate	developmental	5534-09-8	May 15, 1998
Benomyl	developmental, male	17804-35-2	July 1, 1991
Benthiavalicarb-isopropyl	cancer	177406-68-7	July 1, 2008
Benz[a]anthracene	cancer	56-55-3	July 1, 1987
Benzene	cancer	71-43-2	February 27, 1987
Benzene	developmental, male	71-43-2	December 26, 1997
Benzidine [and its salts]	cancer	92-87-5	February 27, 1987
Benzidine-based dyes	cancer	---	October 1, 1992
Benzodiazepines	developmental	---	October 1, 1992
Benzo[b]fluoranthene	cancer	205-99-2	July 1, 1987
Benzo[j]fluoranthene	cancer	205-82-3	July 1, 1987
Benzo[k]fluoranthene	cancer	207-08-9	July 1, 1987
Benzofuran	cancer	271-89-6	October 1, 1990
Benzophenone	cancer	119-61-9	June 22, 2012
Benzo[a]pyrene	cancer	50-32-8	July 1, 1987
Benzotrichloride	cancer	98-07-7	July 1, 1987
Benzphetamine hydrochloride	developmental	5411-22-3	April 1, 1990
Benzyl chloride	cancer	100-44-7	January 1, 1990
Benzyl violet 4B	cancer	1694-09-3	July 1, 1987
Beryllium and beryllium compounds	cancer	---	October 1, 1987
Betel quid with tobacco	cancer	---	January 1, 1990
Betel quid without tobacco	cancer	---	February 3, 2006
Bevacizumab	developmental, female	216974-75-3	March 8, 2019
2,2-Bis(bromomethyl)-1,3-propanediol	cancer	3296-90-0	May 1, 1996
Bis(2-chloroethyl)ether	cancer	111-44-4	April 1, 1988
N,N-Bis(2-chloroethyl)-2-naphthylamine (Chlornapazine)	cancer	494-03-1	February 27, 1987
Bischloroethyl nitrosourea (BCNU) (Carmustine)	cancer	154-93-8	July 1, 1987
Bischloroethyl nitrosourea (BCNU) (Carmustine)	developmental	154-93-8	July 1, 1990
Bis(chloromethyl)ether	cancer	542-88-1	February 27, 1987
Bis(2-chloro-1-methylethyl)ether, technical grade	cancer	---	October 29, 1999
Bisphenol A (BPA)	female	80-05-7	May 11, 2015
~~Bisphenol A (BPA)~~, Delisted April 19, 2013	~~developmental~~	~~80-05-7~~	~~April 11, 2013~~
Bitumens, extracts of steam-refined and air refined	cancer	---	January 1, 1990
Bracken fern	cancer	---	January 1, 1990
Bromacil lithium salt	developmental	53404-19-6	May 18, 1999
Bromacil lithium salt	male	53404-19-6	January 17, 2003
Bromate	cancer	15541-45-4	May 31, 2002
Bromochloroacetic acid	cancer	5589-96-8	April 6, 2010
Bromodichloroacetic acid	cancer	71133-14-7	July 29, 2016
Bromodichloromethane	cancer	75-27-4	January 1, 1990
Bromoethane	cancer	74-96-4	December 22, 2000
Bromoform	cancer	75-25-2	April 1, 1991
1-Bromopropane (1-BP)	cancer	106-94-5	August 5, 2016

Chemical	Type of Toxicity	CAS No.	Date Listed
1-Bromopropane (1-BP)	developmental, female, male	106-94-5	December 7, 2004
2-Bromopropane (2-BP)	female, male	75-26-3	May 31, 2005
Bromoxynil	developmental	1689-84-5	October 1, 1990
Bromoxynil octanoate	developmental	1689-99-2	May 18, 1999
Butabarbital sodium	developmental	143-81-7	October 1, 1992
1,3-Butadiene	cancer	106-99-0	April 1, 1988
1,3-Butadiene	developmental, female, male	106-99-0	April 16, 2004
1,4-Butanediol dimethanesulfonate (Busulfan)	cancer	55-98-1	February 27, 1987
1,4-Butanediol dimethanesulfonate (Busulfan)	developmental	55-98-1	January 1, 1989
Butylated hydroxyanisole	cancer	25013-16-5	January 1, 1990
Butyl benzyl phthalate (BBP)	developmental	85-68-7	December 2, 2005
~~n-Butyl glycidyl ether~~, Delisted April 4, 2014	~~male~~	~~2426-08-6~~	~~August 7, 2009~~
beta-Butyrolactone	cancer	3068-88-0	July 1, 1987
Cacodylic acid	cancer	75-60-5	May 1, 1996
Cadmium	developmental, male	---	May 1, 1997
Cadmium and cadmium compounds	cancer	---	October 1, 1987
Caffeic acid	cancer	331-39-5	October 1, 1994
Captafol	cancer	2425-06-1	October 1, 1988
Captan	cancer	133-06-2	January 1, 1990
Carbamazepine	developmental	298-46-4	January 29, 1999
Carbaryl	cancer	63-25-2	February 5, 2010
Carbaryl	developmental, female, male	63-25-2	August 7, 2009
Carbazole	cancer	86-74-8	May 1, 1996
Carbon black (airborne, unbound particles of respirable size)	cancer	1333-86-4	February 21, 2003
Carbon-black extracts	cancer	---	January 1, 1990
Carbon disulfide	developmental, female, male	75-15-0	July 1, 1989
Carbon monoxide	developmental	630-08-0	July 1, 1989
Carbon tetrachloride	cancer	56-23-5	October 1, 1987
Carboplatin	developmental	41575-94-4	July 1, 1990
N-Carboxymethyl-N-nitrosourea	cancer	60391-92-6	January 25, 2002
Catechol	cancer	120-80-9	July 15, 2003
Ceramic fibers (airborne particles of respirable size)	cancer	---	July 1, 1990
Certain combined chemotherapy for lymphomas	cancer	---	February 27, 1987
Chenodiol	developmental	474-25-9	April 1, 1990
Chloral	cancer	75-87-6	September 13, 2013
Chloral hydrate	cancer	302-17-0	September 13, 2013
Chlorambucil	cancer	305-03-3	February 27, 1987
Chlorambucil	developmental	305-03-3	January 1, 1989
~~Chloramphenicol~~, Delisted January 4, 2013	~~cancer~~	~~56-75-7~~	~~October 1, 1989~~
Chloramphenicol sodium succinate	cancer	982-57-0	September 27, 2013
Chlorcyclizine hydrochloride	developmental	1620-21-9	July 1, 1987
Chlordane	cancer	57-74-9	July 1, 1988
Chlordecone (Kepone)	cancer	143-50-0	January 1, 1988
Chlordecone (Kepone)	developmental	143-50-0	January 1, 1989

Chemical	Type of Toxicity	CAS No.	Date Listed
Chlordiazepoxide	developmental	58-25-3	January 1, 1992
Chlordiazepoxide hydrochloride	developmental	438-41-5	January 1, 1992
Chlordimeform	cancer	6164-98-3	January 1, 1989
Chlorendic acid	cancer	115-28-6	July 1, 1989
Chlorinated paraffins (Average chain length, C12; approximately 60 percent chlorine by weight)	cancer	108171-26-2	July 1, 1989
p-Chloroaniline	cancer	106-47-8	October 1, 1994
p-Chloroaniline hydrochloride	cancer	20265-96-7	May 15, 1998
~~Chlorodibromomethane~~, Delisted October 29, 1999	~~cancer~~	~~124-48-1~~	~~January 1, 1990~~
Chloroethane (Ethyl chloride)	cancer	75-00-3	July 1, 1990
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) (Lomustine)	cancer	13010-47-4	January 1, 1988
1-(2-Chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) Lomustine)	developmental	13010-47-4	July 1, 1990
1-(2-Chloroethyl)-3-(4-methyl-cyclohexyl) -1-nitrosourea (Methyl-CCNU)	cancer	13909-09-6	October 1, 1988
Chloroform	cancer	67-66-3	October 1, 1987
Chloroform	developmental	67-66-3	August 7, 2009
Chloromethyl methyl ether (technical grade)	cancer	107-30-2	February 27, 1987
3-Chloro-2-methylpropene	cancer	563-47-3	July 1, 1989
1-Chloro-4-nitrobenzene	cancer	100-00-5	October 29, 1999
2-Chloronitrobenzene	cancer	88-73-3	September 13, 2019
4-Chloro-*o*-phenylenediamine	cancer	95-83-0	January 1, 1988
Chloroprene	cancer	126-99-8	June 2, 2000
2-Chloropropionic acid	male	598-78-7	August 7, 2009
Chlorothalonil	cancer	1897-45-6	January 1, 1989
p-Chloro-*o*-toluidine	cancer	95-69-2	January 1, 1990
p-Chloro-*o*-toluidine, strong acid salts of	cancer	---	May 15, 1998
5-Chloro-*o*-toluidine and its strong acid salts	cancer	---	October 24, 1997
Chlorotrianisene	cancer	569-57-3	September 1, 1996
p-chloro-*α,α,α*-trifluorotoluene (*para*-Chlorobenzotrifluoride, PCBTF)	cancer	98-56-6	June 28, 2019
Chlorozotocin	cancer	54749-90-5	January 1, 1992
Chlorpyrifos	developmental	2921-88-2	December 15, 2017
~~Chlorsulfuron~~, Delisted June 6, 2014	~~developmental, female, male~~	~~64902-72-3~~	~~May 14, 1999~~
Chromium (hexavalent compounds)	cancer	---	February 27, 1987
Chromium (hexavalent compounds)	developmental, female, male	---	December 19, 2008
Chrysene	cancer	218-01-9	January 1, 1990
C.I. Acid Red 114	cancer	6459-94-5	July 1, 1992
C.I. Basic Red 9 monohydrochloride	cancer	569-61-9	July 1, 1989
C.I. Direct Blue 15	cancer	2429-74-5	August 26, 1997
C.I. Direct Blue 218	cancer	28407-37-6	August 26, 1997
C.I. Disperse Yellow 3	cancer	2832-40-8	February 8, 2013
C.I. Solvent Yellow 14	cancer	842-07-9	May 15, 1998
Ciclosporin (Cyclosporin A; Cyclosporine)	cancer	59865-13-3; 79217-60-0	January 1, 1992

Chemical	Type of Toxicity	CAS No.	Date Listed
Cidofovir	cancer, developmental, female, male	113852-37-2	January 29, 1999
Cinnamyl anthranilate	cancer	87-29-6	July 1, 1989
Cisplatin	cancer	15663-27-1	October 1, 1988
Citrus Red No. 2	cancer	6358-53-8	October 1, 1989
Cladribine	developmental	4291-63-8	September 1, 1996
Clarithromycin	developmental	81103-11-9	May 1, 1997
Clobetasol propionate	developmental, female	25122-46-7	May 15, 1998
Clofibrate	cancer	637-07-0	September 1, 1996
Clomiphene citrate	cancer	50-41-9	May 24, 2013
Clomiphene citrate	developmental	50-41-9	April 1, 1990
Clorazepate dipotassium	developmental	57109-90-7	October 1, 1992
CMNP (pyrazachlor)	cancer	6814-58-0	August 25, 2015
Cobalt metal powder	cancer	7440-48-4	July 1, 1992
Cobalt [II] oxide	cancer	1307-96-6	July 1, 1992
Cobalt sulfate	cancer	10124-43-3	May 20, 2005
Cobalt sulfate heptahydrate	cancer	10026-24-1	June 2, 2000
Cocaine	developmental, female	50-36-2	July 1, 1989
Coconut oil diethanolamine condensate (cocamide diethanolamine)	cancer	---	June 22, 2012
Codeine phosphate	developmental	52-28-8	May 15, 1998
Coke oven emissions	cancer	---	February 27, 1987
Colchicine	developmental, male	64-86-8	October 1, 1992
Conjugated estrogens	cancer	---	February 27, 1987
Conjugated estrogens	developmental	---	April 1, 1990
Creosotes	cancer	---	October 1, 1988
p-Cresidine	cancer	120-71-8	January 1, 1988
Cumene	cancer	98-82-8	April 6, 2010
Cupferron	cancer	135-20-6	January 1, 1988
Cyanazine	developmental	21725-46-2	April 1, 1990
Cycasin	cancer	14901-08-7	January 1, 1988
Cycloate	developmental	1134-23-2	March 19, 1999
~~Cyclohexanol~~, Delisted January 25, 2002	~~male~~	~~108-93-0~~	~~November 6, 1998~~
Cycloheximide	developmental	66-81-9	January 1, 1989
Cyclopenta[cd]pyrene	cancer	27208-37-3	April 29, 2011
Cyclophosphamide (anhydrous)	cancer	50-18-0	February 27, 1987
Cyclophosphamide (anhydrous)	developmental, female, male	50-18-0	January 1, 1989
Cyclophosphamide (hydrated)	cancer	6055-19-2	February 27, 1987
Cyclophosphamide (hydrated)	developmental, female, male	6055-19-2	January 1, 1989
Cyhexatin	developmental	13121-70-5	January 1, 1989
Cytarabine	developmental	147-94-4	January 1, 1989
Cytembena	cancer	21739-91-3	May 15, 1998
D&C Orange No. 17	cancer	3468-63-1	July 1, 1990
D&C Red No. 8	cancer	2092-56-0	October 1, 1990
D&C Red No. 9	cancer	5160-02-1	July 1, 1990
D&C Red No. 19	cancer	81-88-9	July 1, 1990
Dacarbazine	cancer	4342-03-4	January 1, 1988
Dacarbazine	developmental	4342-03-4	January 29, 1999
Daminozide	cancer	1596-84-5	January 1, 1990
Danazol	developmental	17230-88-5	April 1, 1990

Chemical	Type of Toxicity	CAS No.	Date Listed
Dantron (Chrysazin; 1,8-Dihydroxyanthraquinone)	cancer	117-10-2	January 1, 1992
Daunomycin	cancer	20830-81-3	January 1, 1988
Daunorubicin hydrochloride	developmental	23541-50-6	July 1, 1990
2,4-D butyric acid	~~developmental~~, male	94-82-6	June 18, 1999
DDD (Dichlorodiphenyl-dichloroethane)	cancer	72-54-8	January 1, 1989
DDE (Dichlorodi-phenyldichloroethylene)	cancer	72-55-9	January 1, 1989
DDT (Dichlorodi-phenyltrichloroethane)	cancer	50-29-3	October 1 , 1987
o,p'-DDT	developmental, female, male	789-02-6	May 15, 1998
p,p'-DDT	developmental, female, male	50-29-3	May 15, 1998
DDVP (Dichlorvos)	cancer	62-73-7	January 1, 1989
Demeclocycline hydrochloride (internal use)	developmental	64-73-3	January 1, 1992
Des-ethyl atrazine (DEA)	developmental, female	6190-65-4	July 15, 2016
Des-isopropyl atrazine (DIA)	developmental, female	1007-28-9	July 15, 2016
N,N'-Diacetylbenzidine	cancer	613-35-4	October 1, 1989
2,4-Diaminoanisole	cancer	615-05-4	October 1, 1990
2,4-Diaminoanisole sulfate	cancer	39156-41-7	January 1, 1988
2,4-Diamino-6-chloro-*s*-triazine (DACT)	developmental, female	3397-62-4	July 15, 2016
4,4'-Diaminodiphenyl ether (4,4'-Oxydianiline)	cancer	101-80-4	January 1, 1988
2,4-Diaminotoluene	cancer	95-80-7	January 1, 1988
~~Diaminotoluene (mixed)~~, Delisted November 20, 2015	~~cancer~~	---	~~January 1, 1990~~
Diazepam	developmental	439-14-5	January 1, 1992
Diazoaminobenzene	cancer	136-35-6	May 20, 2005
Diazoxide	developmental	364-98-7	February 27, 2001
Dibenz[a,h]acridine	cancer	226-36-8	January 1, 1988
Dibenz[a,j]acridine	cancer	224-42-0	January 1, 1988
Dibenzanthracenes	cancer	---	December 26, 2014
Dibenz[a,c]anthracene	cancer	215-58-7	December 26, 2014
Dibenz[a,h]anthracene	cancer	53-70-3	January 1, 1988
Dibenz[a,j]anthracene	cancer	224-41-9	December 26, 2014
7H-Dibenzo[c,g]carbazole	cancer	194-59-2	January 1, 1988
Dibenzo[a,e]pyrene	cancer	192-65-4	January 1, 1988
Dibenzo[a,h]pyrene	cancer	189-64-0	January 1, 1988
Dibenzo[a,i]pyrene	cancer	189-55-9	January 1, 1988
Dibenzo[a,l]pyrene	cancer	191-30-0	January 1, 1988
Dibromoacetic acid	cancer	631-64-1	June 17, 2008
Dibromoacetonitrile	cancer	3252-43-5	May 3, 2011
1,2-Dibromo-3-chloropropane (DBCP)	cancer	96-12-8	July 1, 1987
1,2-Dibromo-3-chloropropane (DBCP)	male	96-12-8	February 27, 1987
2,3-Dibromo-1-propanol	cancer	96-13-9	October 1, 1994
Di-*n*-butyl phthalate (DBP)	developmental, female, male	84-74-2	December 2, 2005
Dichloroacetic acid	cancer	79-43-6	May 1, 1996
Dichloroacetic acid	developmental, male	79-43-6	August 7, 2009
p-Dichlorobenzene	cancer	106-46-7	January 1, 1989

Chemical	Type of Toxicity	CAS No.	Date Listed
3,3'-Dichlorobenzidine	cancer	91-94-1	October 1, 1987
3,3'-Dichlorobenzidine dihydrochloride	cancer	612-83-9	May 15, 1998
1,1-Dichloro-2,2-bis(*p*-chlorophenyl)ethylene (DDE)	developmental, male	72-55-9	March 30, 2010
1,4-Dichloro-2-butene	cancer	764-41-0	January 1, 1990
3,3'-Dichloro-4,4'-diaminodiphenyl ether	cancer	28434-86-8	January 1, 1988
1,1-Dichloroethane	cancer	75-34-3	January 1, 1990
Dichloromethane (Methylene chloride)	cancer	75-09-2	April 1, 1988
1,4-Dichloro-2-nitrobenzene	cancer	89-61-2	September 13, 2019
2,4-Dichloro-1-nitrobenzene	cancer	611-06-3	September 13, 2019
Dichlorophene	developmental	97-23-4	April 27, 1999
1,2-Dichloropropane	cancer	78-87-5	January 1, 1990
1,3-Dichloro-2-propanol (1,3-DCP)	cancer	96-23-1	October 8, 2010
1,3-Dichloropropene	cancer	542-75-6	January 1, 1989
Dichlorphenamide	developmental	120-97-8	February 27, 2001
Diclofop-methyl	cancer	51338-27-3	April 6, 2010
Diclofop methyl	developmental	51338-27-3	March 5, 1999
Dicumarol	developmental	66-76-2	October 1, 1992
Dieldrin	cancer	60-57-1	July 1, 1988
~~Dienestrol~~, Delisted January 4, 2013	~~cancer~~	~~84-17-3~~	~~January 1, 1990~~
Diepoxybutane	cancer	1464-53-5	January 1, 1988
Diesel engine exhaust	cancer	---	October 1, 1990
Diethanolamine	cancer	111-42-2	June 22, 2012
Di(2-ethylhexyl)phthalate (DEHP)	cancer	117-81-7	January 1, 1988
Di(2-ethylhexyl)phthalate (DEHP)	developmental, male	117-81-7	October 24, 2003
1,2-Diethylhydrazine	cancer	1615-80-1	January 1, 1988
Diethylstilbestrol (DES)	cancer	56-53-1	February 27, 1987
Diethylstilbestrol (DES)	developmental	56-53-1	July 1, 1987
Diethyl sulfate	cancer	64-67-5	January 1, 1988
Diflunisal	developmental, female	22494-42-4	January 29, 1999
~~Diglycidyl ether~~, Delisted April 4, 2014	~~male~~	~~2238-07-5~~	~~August 7, 2009~~
Diglycidyl resorcinol ether (DGRE)	cancer	101-90-6	July 1, 1989
Di-*n*-hexyl phthalate (DnHP)	female, male	84-75-3	December 2, 2005
Dihydroergotamine mesylate	developmental	6190-39-2	May 1, 1997
Dihydrosafrole	cancer	94-58-6	January 1, 1988
Di-isodecyl phthalate (DIDP)	developmental	68515-49-1/26761-40-0	April 20, 2007
Diisononyl phthalate (DINP)	cancer	---	December 20, 2013
Diisopropyl sulfate	cancer	2973-10-6	April 1, 1993
Diltiazem hydrochloride	developmental	33286-22-5	February 27, 2001
3,3'-Dimethoxybenzidine (*o*-Dianisidine)	cancer	119-90-4	January 1, 1988
3,3'-Dimethoxybenzidine dihydrochloride	cancer	20325-40-0	October 1, 1990
3,3'-Dimethoxybenzidine-based dyes metabolized to 3,3'-dimethoxybenzidine	cancer	---	June 11, 2004
N,N-Dimethylacetamide	cancer	127-19-5	September 13, 2019
N,N-Dimethylacetamide	developmental, male	127-19-5	May 21, 2010
4-Dimethylaminoazobenzene	cancer	60-11-7	January 1, 1988

Chemical	Type of Toxicity	CAS No.	Date Listed
trans-2-[(Dimethylamino)methyl-imino]-5-[2-(5-nitro-2-furyl)vinyl]-1,3,4-oxadiazole	cancer	55738-54-0	January 1, 1988
7,12-Dimethylbenz(a)anthracene	cancer	57-97-6	January 1, 1990
3,3'-Dimethylbenzidine (ortho-Tolidine)	cancer	119-93-7	January 1, 1988
3,3'-Dimethylbenzidine-based dyes metabolized to 3,3'-dimethylbenzidine	cancer	---	June 11, 2004
3,3'-Dimethylbenzidine dihydrochloride	cancer	612-82-8	April 1, 1992
Dimethylcarbamoyl chloride	cancer	79-44-7	January 1, 1988
N,N-Dimethylformamide	cancer	68-12-2	October 27, 2017
1,1-Dimethylhydrazine (UDMH)	cancer	57-14-7	October 1, 1989
1,2-Dimethylhydrazine	cancer	540-73-8	January 1, 1988
2,6-Dimethyl-N-nitrosomorpholine (DMNM)	cancer	1456-28-6	February 8, 2013
Dimethyl sulfate	cancer	77-78-1	January 1, 1988
N,N-Dimethyl-*p*-toluidine	cancer	99-97-8	May 2, 2014
Dimethylvinylchloride	cancer	513-37-1	July 1, 1989
m-Dinitrobenzene	male	99-65-0	July 1, 1990
o-Dinitrobenzene	male	528-29-0	July 1, 1990
p-Dinitrobenzene	male	100-25-4	July 1, 1990
3,7-Dinitrofluoranthene	cancer	105735-71-5	August 26, 1997
3,9-Dinitrofluoranthene	cancer	22506-53-2	August 26, 1997
1,3-Dinitropyrene	cancer	75321-20-9	November 2, 2012
1,6-Dinitropyrene	cancer	42397-64-8	October 1, 1990
1,8-Dinitropyrene	cancer	42397-65-9	October 1, 1990
Dinitrotoluene (technical grade)	female, male	---	August 20, 1999
2,4-Dinitrotoluene	cancer	121-14-2	July 1, 1988
2,4-Dinitrotoluene	male	121-14-2	August 20, 1999
2,6-Dinitrotoluene	cancer	606-20-2	July 1, 1995
2,6-Dinitrotoluene	male	606-20-2	August 20, 1999
Dinitrotoluene mixture, 2,4-/2,6-	cancer	---	May 1, 1996
Dinocap	developmental	39300-45-3	April 1, 1990
Dinoseb	developmental, male	88-85-7	January 1, 1989
Di-*n*-propyl isocinchomeronate (MGK Repellent 326)	cancer	136-45-8	May 1, 1996
1,4-Dioxane	cancer	123-91-1	January 1, 1988
Diphenylhydantoin (Phenytoin)	cancer	57-41-0	January 1, 1988
Diphenylhydantoin (Phenytoin)	developmental	57-41-0	July 1, 1987
Diphenylhydantoin (Phenytoin), sodium salt	cancer	630-93-3	January 1, 1988
Direct Black 38 (technical grade)	cancer	1937-37-7	January 1, 1988
Direct Blue 6 (technical grade)	cancer	2602-46-2	January 1, 1988
Direct Brown 95 (technical grade)	cancer	16071-86-6	October 1, 1988
Disodium cyanodithioimido-carbonate	developmental	138-93-2	March 30, 1999
Disperse Blue 1	cancer	2475-45-8	October 1, 1990
Diuron	cancer	330-54-1	May 31, 2002
Doxorubicin hydrochloride (Adriamycin)	cancer	25316-40-9	July 1, 1987
Doxorubicin hydrochloride (Adriamycin)	developmental, male	25316-40-9	January 29, 1999
Doxycycline (internal use)	developmental	564-25-0	July 1, 1990
Doxycycline calcium (internal use)	developmental	94088-85-4	January 1, 1992

Chemical	Type of Toxicity	CAS No.	Date Listed
Doxycycline hyclate (internal use)	developmental	24390-14-5	October 1, 1991
Doxycycline monohydrate (internal use)	developmental	17086-28-1	October 1, 1991
~~2,4-DP (dichloroprop)~~, Delisted January 25, 2002	~~developmental~~	~~120-36-5~~	~~April 27, 1999~~
Emissions from combustion of coal	cancer	---	August 7, 2013
Emissions from high-temperature unrefined rapeseed oil	cancer	---	January 3, 2014
Endrin	developmental	72-20-8	May 15, 1998
Environmental tobacco smoke (ETS)	developmental	---	June 9, 2006
Epichlorohydrin	cancer	106-89-8	October 1, 1987
Epichlorohydrin	male	106-89-8	September 1, 1996
Epoxiconazole	cancer	135319-73-2	April 15, 2011
Ergotamine tartrate	developmental	379-79-3	April 1, 1990
Erionite	cancer	12510-42-8/66733-21-9	October 1, 1988
Estradiol 17B	cancer	50-28-2	January 1, 1988
Estragole	cancer	140-67-0	October 29, 1999
Estrogens, steroidal	cancer	---	August 19, 2005
Estrogen-progestogen (combined) used as menopausal therapy	cancer	---	November 4, 2011
Estrone	cancer	53-16-7	January 1, 1988
Estropipate	cancer, developmental	7280-37-7	August 26, 1997
Ethinylestradiol	cancer	57-63-6	January 1, 1988
Ethionamide	developmental	536-33-4	August 26, 1997
Ethoprop	cancer	13194-48-4	February 27, 2001
Ethyl acrylate	cancer	140-88-5	July 1, 1989
Ethyl alcohol in alcoholic beverages	developmental	---	October 1, 1987
Ethylbenzene	cancer	100-41-4	June 11, 2004
~~Ethyl tert-butyl ether~~, Delisted December 13, 2013	~~male~~	~~637-92-3~~	~~December 18, 2009~~
Ethyl dipropylthiocarbamate	developmental	759-94-4	April 27, 1999
Ethyl-4,4'-dichlorobenzilate	cancer	510-15-6	January 1, 1990
Ethylene dibromide	cancer	106-93-4	July 1, 1987
Ethylene dibromide	developmental, male	106-93-4	May 15, 1998
Ethylene dichloride (1,2-Dichloroethane)	cancer	107-06-2	October 1, 1987
Ethylene glycol (ingested)	developmental	107-21-1	June 19, 2015
Ethylene glycol monoethyl ether	developmental, male	110-80-5	January 1, 1989
Ethylene glycol monoethyl ether acetate	developmental, male	111-15-9	January 1, 1993
Ethylene glycol monomethyl ether	developmental, male	109-86-4	January 1, 1989
Ethylene glycol monomethyl ether acetate	developmental, male	110-49-6	January 1, 1993
Ethyleneimine (Aziridine)	cancer	151-56-4	January 1, 1988
Ethylene oxide	cancer	75-21-8	July 1, 1987
Ethylene oxide	female	75-21-8	February 27, 1987
Ethylene oxide	developmental, male	75-21-8	August 7, 2009
Ethylene thiourea	cancer	96-45-7	January 1, 1988
Ethylene thiourea	developmental	96-45-7	January 1, 1993
~~2-Ethylhexanoic acid~~, Delisted December 13, 2013	~~developmental~~	~~149-57-5~~	~~August 7, 2009~~
Ethyl methanesulfonate	cancer	62-50-0	January 1, 1988
Etodolac	developmental, female	41340-25-4	August 20, 1999

Chemical	Type of Toxicity	CAS No.	Date Listed
Etoposide	cancer	33419-42-0	November 4, 2011
Etoposide	developmental	33419-42-0	July 1, 1990
Etoposide in combination with cisplatin and bleomycin	cancer	---	November 4, 2011
Etretinate	developmental	54350-48-0	July 1, 1987
Fenoxaprop ethyl	developmental	66441-23-4	March 26, 1999
Fenoxycarb	cancer	72490-01-8	June 2, 2000
Filgrastim	developmental	121181-53-1	February 27, 2001
Fluazifop butyl	developmental	69806-50-4	November 6, 1998
Flunisolide	developmental, female	3385-03-3	May 15, 1998
Fluorouracil	developmental	51-21-8	January 1, 1989
Fluoxymesterone	developmental	76-43-7	April 1, 1990
Flurazepam hydrochloride	developmental	1172-18-5	October 1, 1992
Flurbiprofen	developmental, female	5104-49-4	August 20, 1999
Flutamide	developmental	13311-84-7	July 1, 1990
Fluticasone propionate	developmental	80474-14-2	May 15, 1998
Fluvalinate	developmental	69409-94-5	November 6, 1998
Folpet	cancer	133-07-3	January 1, 1989
Formaldehyde (gas)	cancer	50-00-0	January 1, 1988
2-(2-Formylhydrazino)-4-(5-nitro-2-furyl)thiazole	cancer	3570-75-0	January 1, 1988
Fumonisin B_1	cancer	116355-83-0	November 14, 2003
Furan	cancer	110-00-9	October 1, 1993
Furazolidone	cancer	67-45-8	January 1, 1990
Furfuryl alcohol	cancer	98-00-0	September 30, 2016
Furmecyclox	cancer	60568-05-0	January 1, 1990
Fusarin C	cancer	79748-81-5	July 1, 1995
Gallium arsenide	cancer	1303-00-0	August 1, 2008
Ganciclovir	cancer, developmental, male	82410-32-0	August 26, 1997
Ganciclovir sodium	developmental, male	107910-75-8	August 26, 1997
Gasoline engine exhaust (condensates/extracts)	cancer	---	October 1, 1990
Gemfibrozil	cancer	25812-30-0	December 22, 2000
Gemfibrozil	female, male	25812-30-0	August 20, 1999
Gentian violet (Crystal violet)	cancer	548-62-9	November 23, 2018
Glass wool fibers (inhalable and biopersistent)	cancer	---	July 1, 1990
Glu-P-1 (2-Amino-6-methyldipyrido [1,2- a:3',2'-d]imidazole)	cancer	67730-11-4	January 1, 1990
Glu-P-2 (2-Aminodipyrido [1,2-a:3',2'-d]imidazole)	cancer	67730-10-3	January 1, 1990
Glycidaldehyde	cancer	765-34-4	January 1, 1988
Glycidol	cancer	556-52-5	July 1, 1990
Glyphosate	cancer	1071-83-6	July 7, 2017
Goldenseal root powder	cancer	---	December 4, 2015
Goserelin acetate	developmental, female, male	65807-02-5	August 26, 1997
Griseofulvin	cancer	126-07-8	January 1, 1990
Gyromitrin (Acetaldehyde methylformylhydrazone)	cancer	16568-02-8	January 1, 1988
Halazepam	developmental	23092-17-3	July 1, 1990
Halobetasol propionate	developmental	66852-54-8	August 20, 1999

Chemical	Type of Toxicity	CAS No.	Date Listed
Haloperidol	developmental, female	52-86-8	January 29, 1999
Halothane	developmental	151-67-7	September 1, 1996
HC Blue 1	cancer	2784-94-3	July 1, 1989
Heptachlor	cancer	76-44-8	July 1, 1988
Heptachlor	developmental	76-44-8	August 20, 1999
Heptachlor epoxide	cancer	1024-57-3	July 1, 1988
Herbal remedies containing plant species of the genus *Aristolochia*	cancer	---	July 9, 2004
Hexachlorobenzene	cancer	118-74-1	October 1, 1987
Hexachlorobenzene	developmental	118-74-1	January 1, 1989
Hexachlorobutadiene	cancer	87-68-3	May 3, 2011
Hexachlorocyclohexane (technical grade)	cancer	---	October 1, 1987
Hexachlorodibenzodioxin	cancer	34465-46-8	April 1, 1988
Hexachloroethane	cancer	67-72-1	July 1, 1990
2,4-Hexadienal (89% trans, trans isomer; 11% cis, trans isomer)	cancer	---	March 4, 2005
Hexafluoroacetone	developmental, male	684-16-2	August 1, 2008
Hexamethylphosphoramide	cancer	680-31-9	January 1, 1988
Hexamethylphosphoramide	male	680-31-9	October 1, 1994
n-Hexane	male	110-54-3	December 15, 2017
2,5-Hexanedione	male	110-13-4	December 4, 2015
Histrelin acetate	developmental	---	May 15, 1998
Hydramethylnon	developmental, male	67485-29-4	March 5, 1999
Hydrazine	cancer	302-01-2	January 1, 1988
Hydrazine sulfate	cancer	10034-93-2	January 1, 1988
Hydrazobenzene (1,2-Diphenylhydrazine)	cancer	122-66-7	January 1, 1988
Hydrogen cyanide (HCN) and cyanide salts (CN salts)	male	---	July 5, 2013
1-Hydroxyanthraquinone	cancer	129-43-1	May 27, 2005
Hydroxyurea	developmental	127-07-1	May 1, 1997
Idarubicin hydrochloride	developmental, male	57852-57-0	August 20, 1999
Ifosfamide	developmental	3778-73-2	July 1, 1990
Iodine-131	developmental	10043-66-0	January 1, 1989
Imazalil	cancer	35554-44-0	May 20, 2011
Indeno[1,2,3-cd]pyrene	cancer	193-39-5	January 1, 1988
Indium phosphide	cancer	22398-80-7	February 27, 2001
IQ (2-Amino-3-methylimidazo [4,5-f] quinoline)	cancer	76180-96-6	April 1, 1990
Iprodione	cancer	36734-19-7	May 1, 1996
Iprovalicarb	cancer	140923-17-7/ 140923-25-7	June 1, 2007
Iron dextran complex	cancer	9004-66-4	January 1, 1988
Isobutyl nitrite	cancer	542-56-3	May 1, 1996
Isoprene	cancer	78-79-5	May 1, 1996
Isopyrazam	cancer	881685-58-1	July 24, 2012
~~Isosafrole~~, Delisted December 8, 2006	~~cancer~~	~~120-58-1~~	~~October 1, 1989~~
Isotretinoin	developmental	4759-48-2	July 1, 1987
Isoxaflutole	cancer	141112-29-0	December 22, 2000
Kresoxim-methyl	cancer	143390-89-0	February 3, 2012
Lactofen	cancer	77501-63-4	January 1, 1989

Chemical	Type of Toxicity	CAS No.	Date Listed
Lasiocarpine	cancer	303-34-4	April 1, 1988
Lead	developmental, female, male	---	February 27, 1987
Lead and lead compounds	cancer	---	October 1, 1992
Lead acetate	cancer	301-04-2	January 1, 1988
Lead phosphate	cancer	7446-27-7	April 1, 1988
Lead subacetate	cancer	1335-32-6	October 1, 1989
Leather dust	cancer	---	April 29, 2011
Leuprolide acetate	developmental, female, male	74381-53-6	August 26, 1997
Levodopa	developmental	59-92-7	January 29, 1999
Levonorgestrel implants	female	797-63-7	May 15, 1998
Lindane and other hexachloro-cyclohexane isomers	cancer	---	October 1, 1989
Linuron	developmental	330-55-2	March 19, 1999
Lithium carbonate	developmental	554-13-2	January 1, 1991
Lithium citrate	developmental	919-16-4	January 1, 1991
Lorazepam	developmental	846-49-1	July 1, 1990
Lovastatin	developmental	75330-75-5	October 1, 1992
Lynestrenol	cancer	52-76-6	February 27, 2001
Malathion	cancer	121-75-5	May 20, 2016
Malonaldehyde, sodium salt	cancer	24382-04-5	May 3, 2011
Mancozeb	cancer	8018-01-7	January 1, 1990
Maneb	cancer	12427-38-2	January 1, 1990
Marijuana smoke	cancer	---	June 19, 2009
Me-A-alpha-C (2-Amino-3-methyl-9H-pyrido[2,3-b]indole)	cancer	68006-83-7	January 1, 1990
Mebendazole	developmental	31431-39-7	August 20, 1999
Medroxyprogesterone acetate	cancer	71-58-9	January 1, 1990
Medroxyprogesterone acetate	developmental	71-58-9	April 1, 1990
Megestrol acetate	cancer	595-33-5	March 28, 2014
Megestrol acetate	developmental	595-33-5	January 1, 1991
MeIQ (2-Amino-3,4-dimethyl-imidazo[4,5-f]quinoline)	cancer	77094-11-2	October 1, 1994
MeIQx (2-Amino-3,8-dimethyl-imidazo[4,5-f]quinoxaline)	cancer	77500-04-0	October 1, 1994
Melphalan	cancer	148-82-3	February 27, 1987
Melphalan	developmental	148-82-3	July 1, 1990
Menotropins	developmental	9002-68-0	April 1, 1990
Mepanipyrim	cancer	110235-47-7	July 1, 2008
Meprobamate	developmental	57-53-4	January 1, 1992
2-Mercaptobenzothiazole	cancer	149-30-4	October 27, 2017
Mercaptopurine	developmental	6112-76-1	July 1, 1990
Mercury and mercury compounds	developmental	---	July 1, 1990
Merphalan	cancer	531-76-0	April 1, 1988
Mestranol	cancer	72-33-3	April 1, 1988
Metam potassium	cancer	137-41-7	December 31, 2010
Methacycline hydrochloride	developmental	3963-95-9	January 1, 1991
Metham sodium	cancer	137-42-8	November 6, 1998
Metham sodium	developmental	137-42-8	May 15, 1998
Methanol	developmental	67-56-1	March 16, 2012
Methazole	developmental	20354-26-1	December 1, 1999
Methimazole	developmental	60-56-0	July 1, 1990
Methotrexate	developmental	59-05-2	January 1, 1989

Chemical	Type of Toxicity	CAS No.	Date Listed
Methotrexate sodium	developmental	15475-56-6	April 1, 1990
5-Methoxypsoralen with ultraviolet A therapy	cancer	484-20-8	October 1, 1988
8-Methoxypsoralen with ultraviolet A therapy	cancer	298-81-7	February 27, 1987
2-Methylaziridine (Propyleneimine)	cancer	75-55-8	January 1, 1988
Methylazoxymethanol	cancer	590-96-5	April 1, 1988
Methylazoxymethanol acetate	cancer	592-62-1	April 1, 1988
Methyl bromide, as a structural fumigant	developmental	74-83-9	January 1, 1993
Methyl carbamate	cancer	598-55-0	May 15, 1998
Methyl chloride	developmental	74-87-3	March 10, 2000
Methyl chloride	male	74-87-3	August 7, 2009
3-Methylcholanthrene	cancer	56-49-5	January 1, 1990
5-Methylchrysene	cancer	3697-24-3	April 1, 1988
4,4'-Methylene bis(2-chloroaniline)	cancer	101-14-4	July 1, 1987
4,4'-Methylene bis(N,N-dimethyl) benzenamine	cancer	101-61-1	October 1, 1989
4,4'-Methylene bis(2-methylaniline)	cancer	838-88-0	April 1, 1988
4,4'-Methylenedianiline	cancer	101-77-9	January 1, 1988
4,4'-Methylenedianiline dihydrochloride	cancer	13552-44-8	January 1, 1988
Methyleugenol	cancer	93-15-2	November 16, 2001
Methylhydrazine and its salts	cancer	---	July 1, 1992
2-Methylimidazole	cancer	693-98-1	June 22, 2012
4-Methylimidazole	cancer	822-36-6	January 7, 2011
Methyl iodide	cancer	74-88-4	April 1, 1988
Methyl isobutyl ketone	cancer	108-10-1	November 4, 2011
Methyl isobutyl ketone (MIBK)	developmental	108-10-1	March 28, 2014
Methyl isocyanate (MIC)	developmental, female	624-83-9	November 12, 2010
~~Methyl isopropyl ketone~~, Delisted April 4, 2014	~~developmental~~	~~563-80-4~~	~~February 17, 2012~~
Methyl mercury	developmental	---	July 1, 1987
Methylmercury compounds	cancer	---	May 1, 1996
Methyl methanesulfonate	cancer	66-27-3	April 1, 1988
Methyl-n-butyl ketone	male	591-78-6	August 7, 2009
Methyl-n-butyl ketone	developmental	591-78-6	December 4, 2015
2-Methyl-1-nitroanthraquinone (of uncertain purity)	cancer	129-15-7	April 1, 1988
N-Methyl-N'-nitro-N-nitrosoguanidine	cancer	70-25-7	April 1, 1988
N-Methylolacrylamide	cancer	924-42-5	July 1, 1990
N-Methylpyrrolidone	developmental	872-50-4	June 15, 2001
α-Methyl styrene (alpha-Methylstyrene)	cancer	98-83-9	November 2, 2012
~~α-Methyl styrene~~, Delisted April 4, 2014	~~female~~	~~98-83-9~~	~~July 29, 2011~~
Methyltestosterone	developmental	58-18-4	April 1, 1990
Methylthiouracil	cancer	56-04-2	October 1, 1989
Metiram	cancer	9006-42-2	January 1, 1990
Metiram	developmental	9006-42-2	March 30, 1999
Metronidazole	cancer	443-48-1	January 1, 1988
Michler's ketone	cancer	90-94-8	January 1, 1988
Midazolam hydrochloride	developmental	59467-96-8	July 1, 1990
Minocycline hydrochloride (internal use)	developmental	13614-98-7	January 1, 1992

Chemical	Type of Toxicity	CAS No.	Date Listed
Mirex	cancer	2385-85-5	January 1, 1988
Misoprostol	developmental	59122-46-2	April 1, 1990
Mitomycin C	cancer	50-07-7	April 1, 1988
Mitoxantrone hydrochloride	cancer	70476-82-3	January 23, 2015
Mitoxantrone hydrochloride	developmental	70476-82-3	July 1, 1990
Molinate	developmental, female, male	2212-67-1	December 11, 2009
MON 4660 (dichloroacetyl-1- oxa-4-azaspiro(4,5)-decane)	cancer	71526-07-3	March 22, 2011
MON 13900 (furilazole)	cancer	121776-33-8	March 22, 2011
3-Monochloropropane-1,2- diol (3-MCPD)	cancer	96-24-2	October 8, 2010
Monocrotaline	cancer	315-22-0	April 1, 1988
MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)	cancer	113803-47-7	November 4, 2011
5-(Morpholinomethyl)-3- [(5-nitrofurfuryl-idene)- amino]-2-oxazolidinone	cancer	139-91-3	April 1, 1988
Mustard Gas	cancer	505-60-2	February 27, 1987
MX (3-chloro-4-(dichloromethyl) 5-hydroxy-2(5H)-furanone)	cancer	77439-76-0	December 22, 2000
Myclobutanil	developmental, male	88671-89-0	April 16, 1999
beta-Myrcene	cancer	123-35-3	March 27, 2015
Nabam	developmental	142-59-6	March 30, 1999
Nafarelin acetate	developmental	86220-42-0	April 1, 1990
Nafenopin	cancer	3771-19-5	April 1, 1988
Nalidixic acid	cancer	389-08-2	May 15, 1998
Naphthalene	cancer	91-20-3	April 19, 2002
1-Naphthylamine	cancer	134-32-7	October 1, 1989
2-Naphthylamine	cancer	91-59-8	February 27, 1987
Neomycin sulfate (internal use)	developmental	1405-10-3	October 1, 1992
Netilmicin sulfate	developmental	56391-57-2	July 1, 1990
Nickel (Metallic)	cancer	7440-02-0	October 1, 1989
Nickel acetate	cancer	373-02-4	October 1, 1989
Nickel carbonate	cancer	3333-67-3	October 1, 1989
Nickel carbonyl	cancer	13463-39-3	October 1, 1987
Nickel carbonyl	developmental	13463-39-3	September 1, 1996
Nickel compounds	cancer	---	May 7, 2004
Nickel (soluble compounds)	developmental, male	---	October 26, 2018
Nickel hydroxide	cancer	12054-48-7; 12125-56-3	October 1, 1989
Nickelocene	cancer	1271-28-9	October 1, 1989
Nickel oxide	cancer	1313-99-1	October 1, 1989
Nickel refinery dust from the pyrometallurgical process	cancer	---	October 1, 1987
Nickel subsulfide	cancer	12035-72-2	October 1, 1987
Nicotine	developmental	54-11-5	April 1, 1990
Nifedipine	developmental, female, male	21829-25-4	January 29, 1999
Nimodipine	developmental	66085-59-4	April 24, 2001
Niridazole	cancer	61-57-4	April 1, 1988
Nitrapyrin	cancer	1929-82-4	October 5, 2005
Nitrapyrin	developmental	1929-82-4	March 30, 1999
Nitrilotriacetic acid	cancer	139-13-9	January 1, 1988

Chemical	Type of Toxicity	CAS No.	Date Listed
Nitrilotriacetic acid, trisodium salt monohydrate	cancer	18662-53-8	April 1, 1989
5-Nitroacenaphthene	cancer	602-87-9	April 1, 1988
~~5-Nitro-*o*-anisidine~~, Delisted December 8, 2006	~~cancer~~	~~99-59-2~~	~~October 1, 1989~~
o-Nitroanisole	cancer	91-23-6	October 1, 1992
para-Nitroanisole	cancer	100-17-4	September 13, 2019
Nitrobenzene	cancer	98-95-3	August 26, 1997
Nitrobenzene	male	98-95-3	March 30, 2010
4-Nitrobiphenyl	cancer	92-93-3	April 1, 1988
6-Nitrochrysene	cancer	7496-02-8	October 1, 1990
Nitrofen (technical grade)	cancer	1836-75-5	January 1, 1988
2-Nitrofluorene	cancer	607-57-8	October 1, 1990
Nitrofurantoin	male	67-20-9	April 1, 1991
Nitrofurazone	cancer	59-87-0	January 1, 1990
1-[(5-Nitrofurfurylidene)-amino]- 2-imidazolidinone	cancer	555-84-0	April 1, 1988
N-[4-(5-Nitro-2-furyl)-2-thiazolyl] acetamide	cancer	531-82-8	April 1, 1988
Nitrogen mustard (Mechlorethamine)	cancer	51-75-2	January 1, 1988
Nitrogen mustard (Mechlorethamine)	developmental	51-75-2	January 1, 1989
Nitrogen mustard hydrochloride (Mechlorethamine hydrochloride)	cancer	55-86-7	April 1, 1988
Nitrogen mustard hydrochloride (Mechlorethamine hydrochloride)	developmental	55-86-7	July 1, 1990
Nitrogen mustard N-oxide	cancer	126-85-2	April 1, 1988
Nitrogen mustard N-oxide hydrochloride	cancer	302-70-5	April 1, 1988
Nitromethane	cancer	75-52-5	May 1, 1997
2-Nitropropane	cancer	79-46-9	January 1, 1988
1-Nitropyrene	cancer	5522-43-0	October 1, 1990
4-Nitropyrene	cancer	57835-92-4	October 1, 1990
N-Nitrosodi-*n*-butylamine	cancer	924-16-3	October 1, 1987
N-Nitrosodiethanolamine	cancer	1116-54-7	January 1, 1988
N-Nitrosodiethylamine	cancer	55-18-5	October 1, 1987
N-Nitrosodimethylamine	cancer	62-75-9	October 1, 1987
p-Nitrosodiphenylamine	cancer	156-10-5	January 1, 1988
N-Nitrosodiphenylamine	cancer	86-30-6	April 1, 1988
N-Nitrosodi-*n*-propylamine	cancer	621-64-7	January 1, 1988
N-Nitroso-N-ethylurea	cancer	759-73-9	October 1, 1987
N-Nitrosohexamethyleneimine	cancer	932-83-2	November 23, 2018
3-(N-Nitrosomethylamino)-propionitrile	cancer	60153-49-3	April 1, 1990
4-(N-Nitrosomethylamino)-1-(3-pyridyl)1-butanone	cancer	64091-91-4	April 1, 1990
N-Nitrosomethyl-*n*-butylamine	cancer	7068-83-9	December 26, 2014
N-Nitrosomethyl-*n*-decylamine	cancer	75881-22-0	December 26, 2014
N-Nitrosomethyl-*n*-dodecylamine	cancer	55090-44-3	December 26, 2014
N-Nitrosomethylethylamine	cancer	10595-95-6	October 1, 1989
N-Nitrosomethyl-*n*-heptylamine	cancer	16338-99-1	December 26, 2014
N-Nitrosomethyl-*n*-hexylamine	cancer	28538-70-7	December 26, 2014
N-Nitrosomethyl-*n*-nonylamine	cancer	75881-19-5	December 26, 2014
N-Nitrosomethyl-*n*-octylamine	cancer	34423-54-6	December 26, 2014
N-Nitrosomethyl-*n*-pentylamine	cancer	13256-07-0	December 26, 2014

Chemical	Type of Toxicity	CAS No.	Date Listed
N-Nitrosomethyl-*n*-propylamine	cancer	924-46-9	December 26, 2014
N-Nitrosomethyl-*n*-tetradecylamine	cancer	75881-20-8	December 26, 2014
N-Nitrosomethyl-*n*-undecylamine	cancer	68107-26-6	December 26, 2014
N-Nitroso-N-methylurea	cancer	684-93-5	October 1, 1987
N-Nitroso-N-methylurethane	cancer	615-53-2	April 1, 1988
N-Nitrosomethylvinylamine	cancer	4549-40-0	January 1, 1988
N-Nitrosomorpholine	cancer	59-89-2	January 1, 1988
N-Nitrosonornicotine	cancer	16543-55-8	January 1, 1988
N-Nitrosopiperidine	cancer	100-75-4	January 1, 1988
N-Nitrosopyrrolidine	cancer	930-55-2	October 1, 1987
N-Nitrososarcosine	cancer	13256-22-9	January 1, 1988
o-Nitrotoluene	cancer	88-72-2	May 15, 1998
Nitrous oxide	developmental, female	10024-97-2	August 1, 2008
Norethisterone (Norethindrone)	cancer	68-22-4	October 1, 1989
Norethisterone (Norethindrone)	developmental	68-22-4	April 1, 1990
Norethisterone acetate (Norethindrone acetate)	developmental	51-98-9	October 1, 1991
Norethisterone (Norethindrone) /Ethinyl estradiol	developmental	68-22-4 / 57-63-6	April 1, 1990
Norethisterone(Norethindrone)/ Mestranol	developmental	68-22-4 / 72-33-3	April 1, 1990
Norethynodrel	cancer	68-23-5	February 27, 2001
Norgestrel	developmental	6533-00-2	April 1, 1990
Ochratoxin A	cancer	303-47-9	July 1, 1990
Oil Orange SS	cancer	2646-17-5	April 1, 1988
Oral contraceptives, combined	cancer	---	October 1, 1989
Oral contraceptives, sequential	cancer	---	October 1, 1989
Oryzalin	cancer	19044-88-3	September 12, 2008
Oxadiazon	cancer	19666-30-9	July 1, 1991
Oxadiazon	developmental	19666-30-9	May 15, 1998
Oxazepam	cancer	604-75-1	October 1, 1994
Oxazepam	developmental	604-75-1	October 1, 1992
~~p,p'-Oxybis(benzenesulfonyl hydrazide)~~, Delisted December 13, 2013	~~developmental~~	~~80-51-3~~	~~August 7, 2009~~
Oxydemeton methyl	female, male	301-12-2	November 6, 1998
Oxymetholone	cancer	434-07-1	January 1, 1988
Oxymetholone	developmental	434-07-1	May 1, 1997
Oxytetracycline (internal use)	developmental	79-57-2	January 1, 1991
Oxytetracycline hydrochloride (internal use)	developmental	2058-46-0	October 1, 1991
Oxythioquinox (Chinomethionat)	cancer	2439-01-2	August 20, 1999
Oxythioquinox (Chinomethionat)	developmental	2439-01-2	November 6, 1998
Paclitaxel	developmental, female, male	33069-62-4	August 26, 1997
Palygorskite fibers (> 5μm in length)	cancer	12174-11-7	December 28, 1999
Panfuran S	cancer	794-93-4	January 1, 1988
Paramethadione	developmental	115-67-3	July 1, 1990
Parathion	cancer	56-38-2	May 20, 2016
Penicillamine	developmental	52-67-5	January 1, 1991
Pentabromodiphenyl ether mixture [DE-71 (technical grade)]	cancer	---	July 7, 2017
Pentachlorophenol	cancer	87-86-5	January 1, 1990

Chemical	Type of Toxicity	CAS No.	Date Listed
Pentachlorophenol and by-products of its synthesis (complex mixture)	cancer	---	October 21, 2016
Pentobarbital sodium	developmental	57-33-0	July 1, 1990
Pentosan polysulfate sodium	cancer	---	April 18, 2014
Pentostatin	developmental	53910-25-1	September 1, 1996
Perfluorooctane sulfonate (PFOS)	developmental	1763-23-1	November 10, 2017
Perfluorooctanoic acid (PFOA)	developmental	335-67-1	November 10, 2017
Pertuzumab	developmental	380610-27-5	January 27, 2017
Phenacemide	developmental	63-98-9	July 1, 1990
Phenacetin	cancer	62-44-2	October 1, 1989
Phenazopyridine	cancer	94-78-0	January 1, 1988
Phenazopyridine hydrochloride	cancer	136-40-3	January 1, 1988
Phenesterin	cancer	3546-10-9	July 1, 1989
Phenobarbital	cancer	50-06-6	January 1, 1990
Phenolphthalein	cancer	77-09-8	May 15, 1998
Phenoxybenzamine	cancer	59-96-1	April 1, 1988
Phenoxybenzamine hydrochloride	cancer	63-92-3	April 1, 1988
Phenprocoumon	developmental	435-97-2	October 1, 1992
o-Phenylenediamine and its salts	cancer	95-54-5	May 15, 1998
Phenyl glycidyl ether	cancer	122-60-1	October 1, 1990
~~Phenyl glycidyl ether~~, Delisted April 4, 2014	~~male~~	~~122-60-1~~	~~August 7, 2009~~
Phenylhydrazine and its salts	cancer	---	July 1, 1992
o-Phenylphenate, sodium	cancer	132-27-4	January 1, 1990
o-Phenylphenol	cancer	90-43-7	August 4, 2000
Phenylphosphine	~~developmental~~ male	638-21-1	August 7, 2009
PhiP(2-Amino-1-methyl-6-phenylimidazol[4,5-b]pyridine)	cancer	105650-23-5	October 1, 1994
Pimozide	developmental, female	2062-78-4	August 20, 1999
Pioglitazone	cancer	111025-46-8	April 18, 2014
Pipobroman	developmental	54-91-1	July 1, 1990
Pirimicarb	cancer	23103-98-2	July 1, 2008
Plicamycin	developmental	18378-89-7	April 1, 1990
Polybrominated biphenyls	cancer	---	January 1, 1988
Polybrominated biphenyls	developmental	---	October 1, 1994
Polychlorinated biphenyls	cancer	---	October 1, 1989
Polychlorinated biphenyls	developmental	---	January 1, 1991
Polychlorinated biphenyls (containing 60 or more percent chlorine by molecular weight)	cancer	---	January 1, 1988
Polychlorinated dibenzo-*p*-dioxins	cancer	---	October 1, 1992
Polychlorinated dibenzofurans	cancer	---	October 1, 1992
Polygeenan	cancer	53973-98-1	January 1, 1988
Ponceau MX	cancer	3761-53-3	April 1, 1988
Ponceau 3R	cancer	3564-09-8	April 1, 1988
Potassium bromate	cancer	7758-01-2	January 1, 1990
Potassium dimethyldithiocarbamate	developmental	128-03-0	March 30 1999
Pravastatin sodium	developmental	81131-70-6	March 3, 2000
Prednisolone sodium phosphate	developmental	125-02-0	August 20, 1999
Primidone	cancer	125-33-7	August 20, 1999
Procarbazine	cancer	671-16-9	January 1, 1988
Procarbazine hydrochloride	cancer	366-70-1	January 1, 1988
Procarbazine hydrochloride	developmental	366-70-1	July 1, 1990
Procymidone	cancer	32809-16-8	October 1, 1994
Progesterone	cancer	57-83-0	January 1, 1988
Pronamide	cancer	23950-58-5	May 1, 1996

Chemical	Type of Toxicity	CAS No.	Date Listed
Propachlor	cancer	1918-16-7	February 27, 2001
1,3-Propane sultone	cancer	1120-71-4	January 1, 1988
Propargite	cancer	2312-35-8	October 1, 1994
Propargite	developmental	2312-35-8	June 15, 1999
Propazine	developmental, female	139-40-2	July 15, 2016
beta-Propiolactone	cancer	57-57-8	January 1, 1988
Propoxur	cancer	114-26-1	August 11, 2006
Propylene glycol mono-*t*-butyl ether	cancer	57018-52-7	June 11, 2004
Propylene oxide	cancer	75-56-9	October 1, 1988
Propylthiouracil	cancer	51-52-5	January 1, 1988
Propylthiouracil	developmental	51-52-5	July 1, 1990
Pulegone	cancer	89-82-7	April 18, 2014
Pymetrozine	cancer	123312-89-0	March 22, 2011
Pyridine	cancer	110-86-1	May 17, 2002
Pyrimethamine	developmental	58-14-0	January 29, 1999
Quazepam	developmental	36735-22-5	August 26, 1997
Quinoline and its strong acid salts	cancer	---	October 24, 1997
Quizalofop-ethyl	male	76578-14-8	December 24, 1999
Radionuclides	cancer	---	July 1, 1989
Reserpine	cancer	50-55-5	October 1, 1989
Residual (heavy) fuel oils	cancer	---	October 1, 1990
Resmethrin	cancer	10453-86-8	July 1, 2008
Resmethrin	developmental	10453-86-8	November 6, 1998
Retinol/retinyl esters, when in daily dosages in excess of 10,000 IU, or 3,000 retinol equivalents. (NOTE: Retinol/retinyl esters are required and essential for maintenance of normal reproductive function. The recommended daily level during pregnancy is 8,000 IU.)	developmental	---	July 1, 1989
Ribavirin	developmental	36791-04-5	April 1, 1990
Ribavirin	male	36791-04-5	February 27, 2001
Riddelliine	cancer	23246-96-0	December 3, 2004
Rifampin	developmental, female	13292-46-1	February 27, 2001
~~Saccharin~~, Delisted April 6, 2001	~~cancer~~	~~81-07-2~~	~~October 1, 1989~~
~~Saccharin, sodium~~, Delisted January 17, 2003	~~cancer~~	~~128-44-9~~	~~January 1, 1988~~
Safrole	cancer	94-59-7	January 1, 1988
Salted fish, Chinese-style	cancer	---	April 29, 2011
Secobarbital sodium	developmental	309-43-3	October 1, 1992
Sedaxane	cancer	874967-67-6	July 1, 2016
Selenium sulfide	cancer	7446-34-6	October 1, 1989
Sermorelin acetate	developmental	---	August 20, 1999
Shale-oils	cancer	68308-34-9	April 1, 1990
Silica, crystalline (airborne particles of respirable size)	cancer	---	October 1, 1988
Simazine	developmental, female	122-34-9	July 15, 2016
Sodium dimethyldithiocarbamate	developmental	128-04-1	March 30 1999
Sodium fluoroacetate	male	62-74-8	November 6, 1998

Chemical	Type of Toxicity	CAS No.	Date Listed
Soots, tars, and mineral oils(untreated and mildly treated oils and used engine oils)	cancer	---	February 27, 1987
Spirodiclofen	cancer	148477-71-8	October 8, 2010
Spironolactone	cancer	52-01-7	May 1, 1997
Stanozolol	cancer	10418-03-8	May 1, 1997
Sterigmatocystin	cancer	10048-13-2	April 1, 1988
Streptomycin sulfate	developmental	3810-74-0	January 1, 1991
Streptozocin (streptozotocin)	developmental, female, male	18883-66-4	August 20, 1999
Streptozotocin (streptozocin)	cancer	18883-66-4	January 1, 1988
Strong inorganic acid mists containing sulfuric acid	cancer	---	March 14, 2003
Styrene	cancer	100-42-5	April 22, 2016
Styrene oxide	cancer	96-09-3	October 1, 1988
Sulfallate	cancer	95-06-7	January 1, 1988
Sulfasalazine (Salicylazosulfapyridine)	cancer	599-79-1	May 15, 1998
Sulfasalazine (Salicylazosulfapyridine)	male	599-79-1	January 29, 1999
Sulfur dioxide	developmental	7446-09-5	July 29, 2011
Sulindac	developmental, female	38194-50-2	January 29, 1999
Talc containing asbestiform fibers	cancer	---	April 1, 1990
Tamoxifen and its salts	cancer	10540-29-1	September 1, 1996
Tamoxifen citrate	developmental	54965-24-1	July 1, 1990
Temazepam	developmental	846-50-4	April 1, 1990
Teniposide	developmental	29767-20-2	September 1, 1996
Terbacil	developmental	5902-51-2	May 18, 1999
Teriparatide	cancer	52232-67-4	August 14, 2015
Terrazole	cancer	2593-15-9	October 1, 1994
Testosterone and its esters	cancer	58-22-0	April 1, 1988
Testosterone cypionate	developmental	58-20-8	October 1, 1991
Testosterone enanthate	developmental	315-37-7	April 1, 1990
Tetrabromobisphenol A	cancer	79-94-7	October 27, 2017
3,3′,4,4′-Tetrachloroazobenzene	cancer	14047-09-7	July 24, 2012
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	cancer	1746-01-6	January 1, 1988
2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)	developmental	1746-01-6	April 1, 1991
1,1,1,2-Tetrachloroethane	cancer	630-20-6	September 13, 2013
1,1,2,2-Tetrachloroethane	cancer	79-34-5	July 1, 1990
Tetrachloroethylene (Perchloroethylene)	cancer	127-18-4	April 1, 1988
p-a,a,a-Tetrachlorotoluene	cancer	5216-25-1	January 1, 1990
Tetrachlorvinphos	cancer	22248-79-9	May 20, 2016
Tetracycline (internal use)	developmental	60-54-8	October 1, 1991
Tetracyclines (internal use)	developmental	---	October 1, 1992
Tetracycline hydrochloride (internal use)	developmental	64-75-5	January 1, 1991
Tetrafluoroethylene	cancer	116-14-3	May 1, 1997
Tetranitromethane	cancer	509-14-8	July 1, 1990
Thalidomide	developmental	50-35-1	July 1, 1987
Thioacetamide	cancer	62-55-5	January 1, 1988
4,4'-Thiodianiline	cancer	139-65-1	April 1, 1988

Chemical	Type of Toxicity	CAS No.	Date Listed
Thiodicarb	cancer	59669-26-0	August 20, 1999
Thioguanine	developmental	154-42-7	July 1, 1990
Thiophanate methyl	female, male	23564-05-8	May 18, 1999
Thiouracil	cancer	141-90-2	June 11, 2004
Thiourea	cancer	62-56-6	January 1, 1988
Thorium dioxide	cancer	1314-20-1	February 27, 1987
Titanium dioxide (airborne, unbound particles of respirable size)	cancer	---	September 2, 2011
Tobacco, oral use of smokeless products	cancer	---	April 1, 1988
Tobacco smoke	cancer	---	April 1, 1988
Tobacco smoke (primary)	developmental, female, male	---	April 1, 1988
Tobramycin sulfate	developmental	49842-07-1	July 1, 1990
Toluene	developmental	108-88-3	January 1, 1991
	~~female~~	~~108-88-3~~	~~August 7, 2009~~
Toluene diisocyanate	cancer	26471-62-5	October 1, 1989
o-Toluidine	cancer	95-53-4	January 1, 1988
o-Toluidine hydrochloride	cancer	636-21-5	January 1, 1988
~~para-Toluidine~~, Delisted October 29, 1999	~~cancer~~	~~106-49-0~~	~~January 1, 1990~~
Topiramate	developmental	97240-79-4	November 27, 2015
Toxaphene (Polychlorinated camphenes)	cancer	8001-35-2	January 1, 1988
Toxins derived from *Fusarium* Moniliforme (Fusarium verticillioides)	cancer	---	August 7, 2009
Treosulfan	cancer	299-75-2	February 27, 1987
Triadimefon	developmental, female, male	43121-43-3	March 30, 1999
Triamterene	cancer	396-01-0	April 18, 2014
Triazolam	developmental	28911-01-5	April 1, 1990
S,S,S-Tributyl phosphorotrithioate (Tribufos, DEF)	cancer	78-48-8	February 25, 2011
Tributyltin methacrylate	developmental	2155-70-6	December 1, 1999
Trichlormethine (Trimustine hydrochloride)	cancer	817-09-4	January 1, 1992
Trichloroacetic acid	cancer	76-03-9	September 13, 2013
Trichloroethylene	cancer	79-01-6	April 1, 1988
Trichloroethylene	developmental, male	79-01-6	January 31, 2014
2,4,6-Trichlorophenol	cancer	88-06-2	January 1, 1988
1,2,3-Trichloropropane	cancer	96-18-4	October 1,1992
Trientine hydrochloride	developmental	38260-01-4	February 27, 2001
Triforine	developmental	26644-46-2	June 18, 1999
~~1,3,5-Triglycidyl-s-triazinetrione~~, Delisted December 13, 2013	~~male~~	~~2451-62-9~~	~~August 7, 2009~~
Trilostane	developmental	13647-35-3	April 1, 1990
Trimethadione	developmental	127-48-0	January 1, 1991
2,4,5-Trimethylaniline and its strong acid salts	cancer	---	October 24, 1997
Trimethyl phosphate	cancer	512-56-1	May 1, 1996
Trimetrexate glucuronate	developmental	82952-64-5	August 26, 1997
TRIM® VX	cancer	---	May 25, 2018
2,4,6-Trinitrotoluene (TNT)	cancer	118-96-7	December 19, 2008
Triphenyltin hydroxide	cancer	76-87-9	July 1, 1992
Triphenyltin hydroxide	developmental	76-87-9	March 18, 2002

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~~Tris(aziridinyl) *p* benzoquinone (Triaziquone)~~, Delisted December 8, 2006	~~cancer~~	~~68-76-8~~	~~October 1, 1989~~
Tris(1-aziridinyl)phosphine sulfide (Thiotepa)	cancer	52-24-4	January 1, 1988
Tris(2-chloroethyl) phosphate	cancer	115-96-8	April 1, 1992
Tris(2,3-dibromopropyl)phosphate	cancer	126-72-7	January 1, 1988
Tris(1,3-dichloro-2-propyl) phosphate (TDCPP)	cancer	13674-87-8	October 28, 2011
Trp-P-1 (Tryptophan-P-1)	cancer	62450-06-0	April 1, 1988
Trp-P-2 (Tryptophan-P-2)	cancer	62450-07-1	April 1, 1988
Unleaded gasoline (wholly vaporized)	cancer	---	April 1, 1988
Uracil mustard	cancer	66-75-1	April 1, 1988
Uracil mustard	developmental, female, male	66-75-1	January 1, 1992
Urethane (Ethyl carbamate)	cancer	51-79-6	January 1, 1988
Urethane (Ethyl carbamate)	developmental	51-79-6	October 1, 1994
Urofollitropin	developmental	97048-13-0	April 1, 1990
Valproate (Valproic acid)	developmental	99-66-1	July 1, 1987
Vanadium pentoxide (orthorhombic crystalline form)	cancer	1314-62-1	February 11, 2005
Vinblastine sulfate	developmental	143-67-9	July 1, 1990
Vinclozolin	cancer	50471-44-8	August 20, 1999
Vinclozolin	developmental	50471-44-8	May 15, 1998
Vincristine sulfate	developmental	2068-78-2	July 1, 1990
Vinyl bromide	cancer	593-60-2	October 1, 1988
Vinyl chloride	cancer	75-01-4	February 27, 1987
4-Vinylcyclohexene	cancer	100-40-3	May 1, 1996
4-Vinyl-cyclohexene	female, ~~male~~	100-40-3	August 7, 2009
4-Vinyl-1-cyclohexene diepoxide (Vinyl cyclohexene dioxide)	cancer	106-87-6	July 1, 1990
Vinyl cyclohexene dioxide (4-Vinyl-1-cyclohexene diepoxide)	female, ~~male~~	106-87-6	August 1, 2008
Vinyl fluoride	cancer	75-02-5	May 1, 1997
Vinylidene chloride (1,1-Dichloroethylene)	cancer	75-35-4	December 29, 2017
Vinyl trichloride (1,1,2-Trichloroethane)	cancer	79-00-5	October 1, 1990
Vismodegib	developmental, female, male	879085-55-9	January 27, 2017
Warfarin	developmental	81-81-2	July 1, 1987
Wood dust	cancer	---	December 18, 2009
2,6-Xylidine (2,6-Dimethylaniline)	cancer	87-62-7	January 1, 1991
Zalcitabine	cancer	7481-89-2	August 7, 2009
Zidovudine (AZT)	cancer	30516-87-1	December 18, 2009
Zileuton	cancer, developmental, female	111406-87-2	December 22, 2000
~~Zineb~~, Delisted October 29, 1999			

Date: September 13, 2019

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