

FAP 4A4839

ENVIRONMENTAL DEFENSE FUND, BREAST CANCER PREVENTION PARTNERS,
CENTER FOR ENVIRONMENTAL HEALTH, ENVIRONMENTAL WORKING GROUP,
AND LISA LEFFERTS

November 6, 2023

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Office of Food Additive Safety (HFS-200)
Center for Food Safety and Applied Nutrition
U.S. Food and Drug Administration (FDA)
5001 Campus Drive
College Park, MD 20740



Re: Food Additive Petition submitted pursuant to 21 U.S.C. § 348 seeking amended food additive regulations to remove FDA’s approval of four carcinogenic solvents

Dear Dr. Muldoon Jacobs:

Petitioners submit this petition to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. § 348 to amend the food additive regulations to eliminate the agency-approved uses of benzene, ethylene dichloride, methylene chloride, and trichloroethylene to produce food and food ingredients. These substances have been found to induce cancer in humans or animals and, therefore, are not safe pursuant to the Delaney Clause.

Separately, we are submitting a petition to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. § 379e to amend the color additive regulations to eliminate the agency-approved uses of ethylene dichloride, methylene chloride, and trichloroethylene to color or mark food and food ingredients.

These four solvents pose numerous hazards that can harm consumers, workers at the facilities treating the food with the chemicals, and communities living around those facilities (see Table 1). In 2023, EPA proposed to eliminate all uses of trichloroethylene and most uses of methylene chloride regulated under the Toxic Substances Control Act (TSCA), due to their cancer and non-cancer risks (see section VIII below). The fact that FDA already recognizes that these substances have been found to induce cancer (see section II below) should mean the agency can act quickly on the petition.

Table 1: Summary of Cancer Hazards and Other Health Concerns

Chemical	Cancers (Year of First Authoritative Designation)¹	Other Health Effects²
Benzene	<ul style="list-style-type: none">• Leukemia in humans (1980, HHS)• Also associated with lymphoma, other blood cancers, and lung cancer in humans	<ul style="list-style-type: none">• Decreased blood cell count (especially lymphocytes)
Ethylene dichloride	<ul style="list-style-type: none">• Breast, blood vessel (hemangiosarcoma), endometrial, forestomach cancers in rodents (1978, NTP)	<ul style="list-style-type: none">• Kidney effects
Methylene chloride	<ul style="list-style-type: none">• Breast tumors (benign) and liver and lung cancer in rodents (1986, NTP)• Also associated with biliary tract/liver cancer, brain cancer, lymphoma, and myeloma in	<ul style="list-style-type: none">• Liver effects

	humans	
Trichloroethylene	<ul style="list-style-type: none"> • Liver cancer in rodents (1976, NTP) • Kidney cancer in humans (2011, EPA) 	<ul style="list-style-type: none"> • Fetal cardiac malformations • Other developmental effects • Thymus effects
<p>EPA = U.S. Environmental Protection Agency HHS = U.S. Department of Health and Human Services (publishes the Report on Carcinogens) NTP = U.S. National Toxicology Program (tests chemicals for carcinogenicity in mice and rats) ¹ See Appendices for more details. ² Effects used to develop reference doses by EPA's Integrated Risk Information System (IRIS) except for ethylene dichloride where a minimal risk level developed by the Agency for Toxic Substances and Disease Registry (ATSDR) is used because EPA IRIS reference dose not available.</p>		

The FDA-approved uses of one or more of these carcinogenic solvents include making decaffeinated coffee, extracting resins from spices and hops, washing sugar beets, and diluting pesticides (see Table 2).

Table 2: FDA Approved Food Additive Uses and Limits for Carcinogenic Solvents in Food*

FDA approved uses	Ethylene dichloride	Methylene chloride	Trichloroethylene	Benzene
Decaffeinated coffee		10 ppm	25 ppm (10 ppm for instant)	
Hops extract	150 or 5,000 ppm**	5, 150, 5,000, or 22,000 ppm**	150 or 5,000 ppm**	1 ppm
Spice oleoresins*** (not color)	30 ppm	30 ppm	30 ppm	
Wash sugar beets	0.2 ppm in water			
Pesticide dilution	No numerical limit			
<p>* This table does not include indirect and animal feed uses. See Appendix I for additional information. ** Based on method of manufacture and use. *** <u>Oleoresin</u> is semisolid extract composed of resin and essential or fatty oil obtained by evaporation of the solvents used in their production.</p>				

According to an [April 2023 study](#) by Clean Label Project, methylene chloride is commonly used to decaffeinate coffee in many brands despite the availability of water,¹ which is clearly a safer alternative: 7 of 17 (41%) tested samples of decaffeinated coffee contained measurable amounts of methylene chloride.² These results were very similar to Clean Label Project's 2020 study that found methylene chloride in [10 of 25 \(40%\) brands](#).³

Beyond methylene chloride found in decaf coffee, we have not identified additional foods or beverages in the U.S. that contain any of the four carcinogenic solvents resulting from the allowable uses listed in Table 2, but since labelling is not required,⁴ there is no way to tell without rigorous testing. In addition,

¹ Water Only Processing. <https://www.swisswater.com/>. Also see Appendix 2A

² Clean Label Project. More Methylene Chloride! April 2023. https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper_3_2.pdf.

³ Clean Label Project. Decaf Coffee: Our Point of View, 2020. <https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper.pdf>. Also see Are There Chemicals in Your Decaffeinated Coffee? 2023. <https://cleanlabelproject.org/are-there-chemicals-in-your-decaffeinated-coffee/>.

⁴ 21 CFR 173.255(b)(2) requires hops extract to identify the presence of methylene chloride, but there are no labeling requirements on the product purchased by a consumer.

Table 2, but since labelling is not required,⁴ there is no way to tell without rigorous testing. In addition, we have no evidence that FDA knows about current food additive usage of any of these chemicals.

In addition to methylene chloride in decaf coffee, benzene, ethylene dichloride and trichloroethylene are also likely to be present in food. For example, FDA analyzed 70 foods for volatile organic compounds (VOCs) including benzene, ethylene dichloride, and trichloroethylene and detected all three; in fact, all but two foods analyzed contained benzene.⁵ FDA also reported benzene in beverages from testing it conducted in 2005-2007, primarily in those that use benzoate and ascorbic or erythorbic acid.^{6,7} Although FDA did not test carrot juice intended for infants for benzene in its 2006-2007 surveys, a survey in Germany found that carrot juice intended for infants (none of which contained benzoate) had the highest levels of benzene of any beverage tested.⁸

We also analyzed the most recent data (from 2021) in Environmental Protection Agency's (EPA) Toxic Release Inventory, which tracks 650 toxic chemicals that pose a threat to human health and the environment, since all four chemicals are covered by the reporting requirement. Fourteen food and beverage facilities reported producing benzene as a byproduct and releasing some of it into the environment.⁹ We do not know how much benzene produced by those facilities is retained in the food.

Notwithstanding the other risks posed by benzene, ethylene dichloride, methylene chloride, and trichloroethylene, FDA has a duty to remove their approved uses because they are known to induce cancer in animals and/or humans for decades and have no legal place in the food supply. FDA should amend the food additive regulations to eliminate their uses.

I. About the Delaney Clause

Since 1958, the Federal Food, Drug and Cosmetic Act (FFDCA) has stated that “no [food] additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal . . .” (21 U.S.C. § 348(c)(3)(A)).

This requirement, known as the Delaney Clause, is a bright line drawn by Congress that carcinogens are not safe to use in food.¹⁰ This statutory requirement has not been altered in the intervening half-century.

⁴ 21 CFR 173.255(b)(2) requires hops extract to identify the presence of methylene chloride, but there are no labeling requirements on the product purchased by a consumer.

⁵ Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. *J Agric Food Chem* 2003; 51:8120-8127.

⁶ FDA. Questions and Answers on the Occurrence of Benzene in Soft Drinks and Other Beverages. Content current as of 2/25/22. <https://www.fda.gov/food/environmental-contaminants-food/questions-and-answers-occurrence-benzene-soft-drinks-and-other-beverages>.

⁷ FDA. Data on Benzene in Soft Drinks and Other Beverages. Last updated on 3/25/2015. <http://wayback.archive-it.org/7993/20161022184011/http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm055815.htm>.

⁸ Lachenmeier DW, Reusch H, Sproll C et al. Occurrence of Benzene as a Heat-Induced Contaminant of Carrot Juice for Babies in a General Survey of Beverages. *Food Add Contam* 2008;25(10):1216-1224.

⁹ EPA TRI Explorer, 2021 National Analysis Dataset, Releases: Facility Report for Benzene, 2021. https://enviro.epa.gov/triexplorer/release_fac?p_view=USFA&trilib=TRIQ2&sort=RE_TOLBY&sort_fmt=2&state=All+states&county=All+counties&chemical=0000071432&industry=311&industry=3121&year=2021&tab_rpt=1&fld=RELLBY&fld=TSFDSP.

¹⁰ *Public Citizen v. Young*, 831 F.2d 1108, 1122 (D.C. Cir. 1987); *Les v. Reilly*, 968 F.2d 985, 989 (9th Cir. 1992)

II. FDA Recognizes These Four Chemicals as Carcinogens

FDA itself already recognizes that these substances are carcinogenic.

FDA stated, “**Benzene** is a carcinogen that can cause cancer in humans”¹¹ and “**Benzene** is a known human carcinogen that causes leukemia and other blood disorders.”¹²

FDA considers **benzene and ethylene dichloride**, to be “Class 1” solvents, meaning that they “should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect.”^{13,14} Yet, illogically, FDA permits these substances to be employed as food additives.

- For **benzene**, FDA identifies it as a Class 1 solvent with the concern “carcinogen.”¹⁵ An FDA document entitled “Appendix 4: Toxicological Data for Class I Solvents” and also identified as a support document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) Guideline states, “There is sufficient evidence to establish that **benzene** is a human carcinogen (lymphatic and hematopoietic cancers). In animal studies, Zymbal gland tumors, preputial gland tumors, skin carcinomas, mammary gland tumors and leukemia are observed.”¹⁶ We note that the benzene entry in this document references the International Agency for Research on Cancer (IARC), Agency for Toxic Substances and Disease Registry (ATSDR), and EPA, implying that FDA and ICH recognize these agencies as authorities.
- For **ethylene dichloride** (1,2-dichloroethane) the same document states, “Forestomach cancer, hemangiosarcoma, breast cancer, uterine cancer and respiratory cancer were found in rats or mice after gavage treatment.” It also says, “possible human carcinogen (IARC 2B).” This entry references IARC and National Cancer Institute (NCI), now identified as an NTP¹⁷ study.¹⁸

(providing that “[t]hroughout its 30-year history, the Delaney clause has been interpreted as an absolute bar to all carcinogenic food additives” and that “. . . Congress has repeatedly ratified a strict interpretation of the Delaney clause” (internal citations omitted)).

¹¹ FDA. Questions and Answers on the Occurrence of Benzene in Soft Drinks and Other Beverages. Content current as of 2/25/2022. <https://www.fda.gov/food/environmental-contaminants-food/questions-and-answers-occurrence-benzene-soft-drinks-and-other-beverages>.

¹² FDA. FDA Alerts Drug Manufacturers to the Risk of Benzene Contamination in Certain Drugs. Content current as of 12/23/2022. <https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs>.

¹³ FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.

¹⁴ FDA. Center for Drug Evaluation and Research. Office of Pharmaceutical Quality. Manual of Policies and Procedures. Acceptance Criteria for Residual Solvents. 2022. <https://www.fda.gov/media/75126/download>.

¹⁵ FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.

¹⁶ FDA. Appendix 4: Toxicological Data for Class 1 Solvents (no date, draft 7). <https://www.fda.gov/media/71738/download>. Also available as ICH Guideline Q3C (R6) on Impurities – Support Document 1: Toxicological Data for Class I Solvents. European Medicines Agency, October 2018. at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.

¹⁷ NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity (CAS No. 107-06-2), Technical Report Series No. 55, 1978. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055/index.html>.

¹⁸ FDA. Appendix 4: Toxicological Data for Class 1 Solvents (no date, draft 7).

FDA proposed a rule in 1977 to amend the food additive regulations by prohibiting **trichloroethylene** in human food,¹⁹ based on studies by NCI showing the chemical caused cancer in laboratory animals. It stated,

“Having evaluated the available data, the Commissioner concludes that the National Cancer Institute report demonstrates that trichloroethylene is a carcinogen in test animals. Accordingly, under the provisions of section 409(c)(3)(A) of the act, which is known as the Delaney clause (21 U.S.C. 348(c)(3)(A)), its use as a food additive may no longer be approved.”²⁰ [emphasis added]

The cancer evidence on trichloroethylene led FDA²¹ to:

- propose rules to amend the food additive regulations to delete provisions for use of trichloroethylene in the manufacture of foods and food contact surfaces;
- propose rules to amend the color additive regulations to delete trichloroethylene in the manufacture of color additives;
- declare that any human or animal drug product containing trichloroethylene is a new drug or new animal drug and deemed to be misbranded;
- declare that any cosmetic product containing trichloroethylene is deemed to be adulterated; and
- declare that food or animal feed containing trichloroethylene is deemed to be adulterated.

However, FDA withdrew the proposed rules on trichloroethylene in 1991, along with many others.²² FDA did not indicate specifically why it withdrew the trichloroethylene or other proposed rules, but explained that proposals were withdrawn in many cases because the proposals were superseded by subsequent actions or events or no longer reflected the agency’s regulatory objectives or priorities, and that in other cases, enough time had elapsed that it would be appropriate to publish a new proposal or tentative final rule before proceeding to final action. Meanwhile, decades later, FDA still permits trichloroethylene for these uses.

FDA described methylene chloride as “a carcinogenic chemical” in its 2003 final rule permitting the use of acesulfame potassium (it is a potential impurity of acesulfame potassium).²³

FDA concluded in 1989 that the use of **methylene chloride** in cosmetic products poses a significant cancer risk to consumers and has deemed cosmetics containing methylene chloride as an ingredient to

<https://www.fda.gov/media/71738/download>. Also available as ICH Guideline Q3C (R6) on Impurities – Support Document 1: Toxicological Data for Class I Solvents. European Medicines Agency, October 2018. at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.

¹⁹ FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).

²⁰ FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).

²¹ FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).

²² FDA, Withdrawal of Certain Pre-1986 Proposed Rules; Final Action. 56 Fed. Reg. 67440 (December 30, 1991).

²³ FDA. Food Additives Permitted for Direct Addition to Food for Human Consumption: Acesulfame Potassium. 68 Fed. Reg. 75411 (December 31, 2003),

be adulterated and subject to regulatory action, based on an NTP inhalation study in mice and exposure estimates from its use in hair sprays.²⁴ Yet it continues to be allowed in food.

III. U.S. Government Testing Establishes the Carcinogenicity of These Four Chemicals

All four chemical have been tested as directed by the Department of Health and Human Services' (HHS) and found to induce cancer in animals.²⁵ NTP made these findings pursuant to a Congressional directive at 42 U.S.C. § 241 to the HHS Secretary to conduct these types of tests. The Secretary established NTP to perform this work. See Appendix 3 Parts 2 and 3 for details.

IV. The Carcinogenicity of These Four Chemicals is Widely Recognized by Authoritative Bodies

- The U.S. Report on Carcinogens recognizes the carcinogenicity of all four chemicals (see Appendix 3 Parts 2 and 3 for details). Congress mandated at 42 U.S.C. § 241(b)(4) that the Secretary of HHS publish a biennial report listing substances: 1) which are known to be carcinogens or may reasonably be anticipated to be carcinogens, and 2) to which a significant number of persons residing in the United States are exposed. With the Secretary's approval, NTP has designated **benzene** and **trichloroethylene** as "known to be a human carcinogen," and **ethylene dichloride (1,2-dichloroethane)** and **methylene chloride (dichloromethane)** as "reasonably anticipated to be a human carcinogen," in its Report on Carcinogens.²⁶
- IARC recognizes the carcinogenicity of all four chemicals. Specifically, it designates two as Group 1, or "carcinogenic to humans" (**benzene** and **trichloroethylene**, based on sufficient evidence in animals and humans); one as Group 2A, or "probably carcinogenic to humans" (**methylene chloride** (dichloromethane), based on limited evidence in humans, sufficient evidence in animals, and other strong relevant evidence), and one as Group 2B, or "Possibly carcinogenic to humans," (**ethylene dichloride** (1,2-dichloroethane) based on sufficient animal evidence.²⁷ IARC is the specialized cancer agency of the World Health Organization (WHO) that was established in 1965. It provides scientific reviews and evaluations of evidence on the carcinogenicity of a wide range of agents and publishes its designations in Monographs on the Evaluation of Carcinogenic Hazards to Humans.²⁸ The U.S. President's Cancer Panel described IARC's monographs on carcinogenesis as "the 'gold standard' in evaluating evidence on cancer-causation."²⁹ (See Appendix 3 Parts 2 and 3 for more details.)
- EPA recognizes the carcinogenicity of all four chemicals. Specifically, it designates two as carcinogenic to humans (**benzene**, **trichloroethylene**), one as a probable human carcinogen (**ethylene dichloride** (1,2-dichloroethane)), and one as likely to be carcinogenic to humans

²⁴ 21 CFR 700.19.

²⁵ See Appendices 1 and 3 for details.

²⁶ NTP, Report on Carcinogens, Fifteenth Edition, 2021. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html>.

²⁷ See Appendix 3 Parts 2 and 3 for more details.

²⁸ IARC, Preamble to the IARC Monographs (amended January 2019), and IARC Mission, accessed April 18, 2023 at <https://monographs.iarc.who.int/iarc-mono-graphs-preamble-preamble-to-the-iarc-mono-graphs/> and <https://www.iarc.who.int/iarc-mission/>.

²⁹ The President's Cancer Panel, Reducing Environmental Cancer Risk: What We Can Do Now, 2008-2009 Annual Report of the President's Cancer Panel, 2010. https://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf

(**methylene chloride** (dichloromethane) (see Appendix 3 Parts 2 and 3). Based on the cancer evidence, EPA has established a goal of zero for the presence of these carcinogens in drinking water.³⁰

- ATSDR recognizes the carcinogenicity of all four chemicals. It has completed Tox Profiles for **benzene**,³¹ **methylene chloride**,³² and **trichloroethylene**,³³ and has issued a Tox Profile draft for public comment on **ethylene dichloride**,³⁴ all of which affirm the carcinogenicity of these substances. It also recently published a **Systematic Evidence Map for methylene chloride**³⁵ which provides an overview of new evidence published since the Tox Profile was published and which continues to affirm the carcinogenicity of methylene chloride (see Appendix 3 Parts 2 and 3).
- California’s Office of Environmental Health Hazard Assessment (OEHHA) recognizes the carcinogenicity of all four chemicals (see Appendix 3 Parts 2 and 3) and requires warning to consumers as part of the Safe Drinking Water and Toxic Enforcement Act of 1986 (also known as Proposition 65).³⁶

The American Cancer Society lists all four chemicals on its “Known and Probable Human Carcinogens” webpage, based on “the determinations of other respected agencies” including IARC and NTP.³⁷

In addition, the World Health Organization has identified benzene as one of ten chemicals of public health concern,³⁸ and the Joint Food and Agriculture Organization (FAO)/WHO Expert Committee on Food Additives (JECFA) considers benzene and ethylene dichloride (1,2-dichloroethane), “not suitable for use as a food additive.”³⁹

V. FDA Need Not Conduct Additional Hazard Analyses of the Carcinogenicity of These Four Chemicals

We note that, under the FFDCA, there is no reason for FDA to conduct additional hazard analyses of the

³⁰ EPA. National Primary Drinking Water Regulations. Last updated on January 9, 2023.

<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations#Organic>.

³¹ ATSDR. Toxicological Profile for Benzene. 2007.

<https://wwwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.

³² ATSDR Toxicological Profile for Methylene Chloride. 2000.

<https://wwwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

³³ ATSDR. Toxicological Profile for Trichloroethylene. 2019.

<https://wwwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.

³⁴ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022.

<https://wwwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

³⁵ ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022.

<https://wwwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

³⁶ OEHHA, Proposition 65, accessed on April 18, 2023, at <http://www.oehha.ca.gov/prop65.html>.

³⁷ American Cancer Society. Known and Probable Human Carcinogens. Last revised July 8, 2022.

<https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/known-and-probable-human-carcinogens.html>.

³⁸ World Health Organization. 10 Chemicals of Public Health Concern. 2020. <https://www.who.int/news-room/photo-story/photo-story-detail/10-chemicals-of-public-health-concern>.

³⁹ World Health Organization. Evaluation of Certain Food Additives. Twenty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series 648, 1980.

https://apps.who.int/iris/bitstream/handle/10665/41403/WHO_TRS_648.pdf;jsessionid=35B181F8B1C12C4DD441B240A6E1CCE9?sequence=1.

carcinogenicity of these substances given this clear body of evidence. FDA has already determined NTP studies constitute “tests appropriate for the evaluation of the safety of food additives” under the Delaney Clause in its 2018 decision on carcinogenic flavors.⁴⁰ Furthermore, as already mentioned and as further discussed later in this petition, FDA already recognizes the carcinogenicity of these chemicals, and a wealth of additional authoritative analyses of the substances’ carcinogenicity satisfy the Delaney Clause standards.

VI. All Four Chemicals Are Food Additives and Appear in the Food Additive Regulations

FDA allows these chemicals to be used as solvents in its food additives regulations at 21 CFR §§ 172.560, 172.710, 173.230, 173.255, 173.290, and 173.315. Because the solvents are added to food or can reasonably be expected to become a component in a food product when used as prescribed by these regulations, they are food additives and subject to the Delaney Clause.

A food additive is defined in 21 CFR § 170.3 Definitions paragraph (e)(1):

“Food additives includes all substances not exempted by section 201(s) of the act, the intended use of which results or may reasonably be expected to result, directly or indirectly, either in their becoming a component of food or otherwise affecting the characteristics of food. ...A substance that does not become a component of food, but that is used, for example, in preparing an ingredient of the food to give a different flavor, texture, or other characteristic in the food, may be a food additive.”

Section 201(s) of the FFDCA states:

“The term “food additive” means any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food (including any substance intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food; and including any source of radiation intended for any such use), if such substance is not generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use; except that such term does not include—

- (1) a pesticide chemical residue in or on a raw agricultural commodity or processed food; or
- (2) a pesticide chemical; or
- (3) a color additive; or
- (4) any substance used in accordance with a sanction or approval granted prior to the enactment of this paragraph 4 pursuant to this Act, the Poultry Products Inspection Act (21 U.S.C. 451 and the following) or the Meat Inspection Act of March 4, 1907 (34 Stat. 1260), as amended and extended (21 U.S.C. 71 and the following);
- (5) a new animal drug; or
- (6) an ingredient described in paragraph (ff) in, or intended for use in, a dietary supplement.”

These chemicals are listed in the food additive regulations (see Appendices 1 and 4) and their intended

⁴⁰ FDA, Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. 83 Fed Reg 50490 (October 9, 2018).

use results or may reasonably be expected to result in their becoming a component of food.

Specifically, all four chemicals appear in 21 CFR Part 172, "Food Additives Permitted for Direct Addition to Food for Human Consumption," specifically under § 172.560, "Modified Hop Extract." That section provides a limit on their residues in the flavoring agent modified hop extract resulting from their use as a solvent during its manufacture, thereby providing further indication that their use may reasonably be expected to result in their becoming a component of food. Thus, the chemicals are used as food additives.

Ethylene dichloride also appears under 21 CFR Part 172, "Food Additives Permitted for Direct Addition to Food for Human Consumption," in § 172.710, "Adjuvants for Pesticide Use Dilutions." That section lists surfactants and related adjuvants that may be added to pesticide use dilutions by a grower or applicant prior to application to the growing crop. Thus, the chemical is used as a food additive.

Ethylene dichloride, methylene chloride, and trichloroethylene also appear under 21 CFR Part 173, "Secondary Direct Food Additives Permitted in Food for Human Consumption" in:

- § 173.230, "Ethylene dichloride," establishes a tolerance for the chemical in spice oleoresins when present therein as a residue from the extraction of spice, thereby providing further indication that its use may reasonably be expected to result in its becoming a component of food. Thus, the chemical is used as a food additive.
- § 173.255, "Methylene chloride," states it may be present in food under specified conditions. Specifically, it is permitted in spice oleoresins as a residue from the extraction of spice, in hops extract as a residue from the extraction of hops, and in coffee as a residue from its use as a solvent in the extraction of caffeine from green coffee beans. In all three cases, limits on the residues are provided (for its use in coffee, limits are provided in decaffeinated roasted coffee and instant coffee), thereby providing further indication that its use may reasonably be expected to result in its becoming a component of food. Thus, the chemical is used as a food additive.
- § 173.290, "Trichloroethylene," establishes tolerances for residues resulting from its use as a solvent in the manufacture of foods, specifically decaffeinated ground coffee, instant coffee, and spice oleoresins, thereby providing further indication that its use may reasonably be expected to result in its becoming a component of food. Thus, the chemical is used as a food additive.

Finally, ethylene dichloride also appears under 21 CFR Part 173, "Secondary Direct Food Additives Permitted in Food for Human Consumption," in § 173.315, "Chemicals Used in Washing or to Assist in the Peeling of Fruits and Vegetables." Specifically, it is listed in paragraph (a)(4), for use in flume water for washing sugar beets prior to the slicing operation. A limitation for the level of the substance in the flume water is provided, thereby providing further indication that its use may reasonably be expected to result in its becoming a component of food. Thus, the chemical is used as a food additive.

There are also indirect uses (see Appendix I) which are not covered by this petition.

VII. All Four Chemicals Are Present in Food⁴¹

Although we are not taking the position or implying that proof of the substances' presence in food is a burden petitioners must meet, we present evidence below that all four chemicals are present in food.

As mentioned previously, an April 2023 study by Clean Label Project found measurable levels of methylene chloride in 7 of 17 (41%) samples of decaffeinated coffees tested. All samples were reported at below the 10 ppm limit.⁴² The study followed up on Clean Label Projects's 2020 study that found methylene chloride in 10 of 25 (40%) samples of decaffeinated coffees tested.⁴³ Levels of methylene chloride were 10-100 times higher in 2023 compared to 2020. The highest levels in the 2023 testing were products sold under the Publix, Dunkin', and Wegmans brands. Products without detected levels of methylene chloride (<0.03 ppm) were sold under the McCafe, The Coffee Bean & Tea Leaf, Sprouts Farmers Marker, Starbucks, and Wegmans brands. In both studies, best-seller lists found on Amazon, Walmart, and Target were used, and samples were procured using Clean Label Project's Consumer Chain of Custody Sampling and Testing Process and obtained from local co-ops, national retailers, and marketplace websites to replicate the consumer shopping experience. An accredited analytical chemistry laboratory was used and testing was conducted blind using Purge and Trap Gas Chromatography Mass Spectrometry.

Except for methylene chloride in coffee, the lack of labeling requirements and paucity of testing means the extent to which FDA's approved uses of these four chemicals contribute to their documented presence in the U.S. food supply is not known. They may also find their way into food through many routes in addition to the permitted uses that are the subject of this petition, including from residues in color additives resulting from permitted uses (the subject of a companion petition we are submitting), packaging, the storage environment, contaminated water used in production or processing, as products of combustion, from chlorination of processing water, microwaving, irradiation, or the degradation of food additives/components such as benzoates.^{44,45}

FDA analyzed 70 foods for VOCs including benzene, ethylene dichloride, and trichloroethylene and detected all three in at least some foods. All foods analyzed contained benzene except American cheese and vanilla ice cream, with the highest levels in fully cooked ground beef (190 ppb), carbonated cola (138 ppb), raw banana (132 ppb), and coleslaw with dressing (102 ppb). That fully cooked ground beef was the food with the highest level of benzene among the foods tested by FDA is noteworthy since it indicates that volatile chemicals such as benzene are present in food following cooking/processing. The highest levels of trichloroethylene reported by FDA were in potato chips (140 ppb) and beef frankfurters (105 ppb). Ethylene dichloride was reported in only one food: eight samples of fruit-flavored cereal, with levels ranging from 16-144 ppb.⁴⁶

FDA also reported benzene in beverages in testing it conducted in 2006-2007, primarily in those that use

⁴¹ This section is not meant to be an exhaustive review of the literature but instead provides examples of key studies illustrating that all four carcinogens are present in food.

⁴² Clean Label Project. More Methylene Chloride! April 2023. https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper_3_2.pdf.

⁴³ Clean Label Project. Decaf Coffee: Our Point of View. 2020. <https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper.pdf>.

⁴⁴ Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. *J Agric Food Chem* 2003; 51:8120-8127,

⁴⁵ Salviano dos Santos VP, Salgado AM, Torres AG, Pereira KS. Benzene as a Chemical Hazard in Processed Foods. *Int J Food Sci* 2015;2015:545640.

⁴⁶ Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. *J Agric Food Chem* 2003; 51:8120-8127,

benzoate and ascorbic or erythorbic acid.^{47,48} Although FDA did not test carrot juice intended for infants for benzene in its 2006-2007 surveys, a survey in Germany of 451 beverage samples found that carrot juice intended for infants (none of which contained benzoate) had the highest levels of benzene of any beverage tested.⁴⁹

We also analyzed the most recent data (from 2021) in Environmental Protection Agency's (EPA) Toxic Release Inventory, since all four chemicals are covered by the reporting requirement. Companies that produce more than 25,000 pounds or process more than 10,000 pounds of a chemical in a calendar year are required to submit reports to EPA. We only found reports for benzene. Fourteen food and beverage facilities⁵⁰ reported benzene:

- Five ADM facilities in Cedar Rapids and Clinton, Iowa; Columbus, Nebraska; Decatur, Illinois; and Marshall, Minnesota;
- Three Cargill facilities in Eddyville and Fort Dodge, Iowa and Blair, Nebraska;
- Two Grain Processing Corp facilities in Muscatine, Iowa and Washington, Indiana;
- Pacific Ethanol facility in Perkin, Illinois;
- Poet Holding facility in Groton, South Dakota;
- Primary Products Ingredients Americas facility in Loudon, Tennessee; and
- Sugar Cane Growers Cooperative of Florida in Belle Glade, Florida.

These facilities released a total of 14,434 pounds of benzene. The largest releases to the environment from a single facility were from the Sugar Cane Growers Cooperative of Florida (6,589 pounds) and ADM's Decatur Complex (4,535 pounds). We do not know how much benzene produced by those facilities is retained in the foods or beverages, nor to what extent those communities are impacted by benzene.

VIII. Hazards In Addition to Cancer

Although there is no need to establish non-cancer health risks for the purposes of this petition, petitioners note that EPA recognizes that these chemicals cause cancer as well as other serious health impacts:

- EPA considers all four chemicals to be hazardous air pollutants.⁵¹ Hazardous air pollutants are those known to cause cancer and other serious health impacts.⁵²
- EPA determined that uses of two of these chemicals, methylene chloride and trichloroethylene,

⁴⁷ FDA. Questions and Answers on the Occurrence of Benzene in Soft Drinks and Other Beverages. Content current as of 2/25/22. <https://www.fda.gov/food/environmental-contaminants-food/questions-and-answers-occurrence-benzene-soft-drinks-and-other-beverages>.

⁴⁸ FDA. Data on Benzene in Soft Drinks and Other Beverages. Last updated on 3/25/2015. <http://wayback.archive-it.org/7993/20161022184011/http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm055815.htm>.

⁴⁹ Lachenmeier DW, Reusch H, Sproll C et al. Occurrence of Benzene as a Heat-Induced Contaminant of Carrot Juice for Babies in a General Survey of Beverages. Food Add Contam Part A Chem Anal Contr Exp Risk Assess 2008;25(10):1216-1224.

⁵⁰ EPA. TRI Explorer, 2021 National Analysis Dataset, Releases: Facility Report for Benzene. 2023. https://enviro.epa.gov/triexplorer/release_fac?p_view=USFA&trilib=TRIQ2&sort=RE_TOLBY&sort_fmt=2&state=All+states&county=All+counties&chemical=0000071432&industry=311&industry=3121&year=2021&tab_rpt=1&fld=RELLBY&fld=TSFDS.

⁵¹ EPA. Initial List of Hazardous Air Pollutants with Modifications. Last updated on December 19, 2022. <https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications>.

⁵² EPA. Hazardous Air Pollutants. Last updated on February 9, 2023. <https://www.epa.gov/haps>.

pose an unreasonable risk to human health, including the health of workers and occupational non-users (workers nearby but not in direct contact), based on the cancer evidence as well as neurotoxicity and liver effects.⁵³

- EPA also designated ethylene dichloride (1,2-dichloroethane) as a high priority for evaluation, and it is currently undergoing risk evaluation.⁵⁴ EPA has identified immune and neurological effects in addition to cancer as potential human health hazards associated with ethylene dichloride in its final scope document.⁵⁵
- In May 2023, EPA proposed to address the unreasonable risk to human health posed by methylene chloride, as documented in its risk evaluation that included cancer and non-cancer risks, by prohibiting manufacturing, processing, and distribution of methylene chloride for all consumer uses and most industrial and commercial uses of methylene chloride regulated under TSCA.⁵⁶
- In October 2023, EPA proposed to address the unreasonable risk to human health posed by trichloroethylene, as documented in its risk evaluation that included cancer and non-cancer risks, by prohibiting manufacturing, processing, and distribution for all uses of trichloroethylene regulated under TSCA.⁵⁷
- EPA has established reference doses (RfDs) for benzene, methylene chloride, and trichloroethylene for non-cancer effects. EPA defines a RfD as “An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.” RfDs are generally used in EPA’s noncancer health assessments.⁵⁸
 - For benzene, the RfD of 0.004 mg/kg of body weight per day is based on decreased lymphocyte count.⁵⁹ EPA states, “Benzene is toxic by all routes of administration.

⁵³ EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health (Last updated January 9, 2023) <https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health> and Final Risk Evaluation for Methylene Chloride (Last updated on May 11, 2023), <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-methylene-chloride> and https://www.epa.gov/system/files/documents/2022-11/MC_Final%20Revised%20RD_10.26.22-final%20%281%29.pdf.

⁵⁴ EPA. EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health (Last updated January 9, 2023) <https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health> and Final Risk Evaluation for Methylene Chloride (Last updated on May 11, 2023) <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-methylene-chloride> and Risk Evaluation for 1,2-Dichloroethane (Last updated on May 25, 2023) .

⁵⁵ EPA. Final Scope of the Risk Evaluation for 1,2-Dichloroethane. August 2020. https://www.epa.gov/sites/default/files/2020-09/documents/casrn_107-06-2_12-dichloroethane_final_scope.pdf.

⁵⁶ EPA. Risk Management for Methylene Chloride. Updated June 7, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-methylene-chloride> and 88 Fed. Reg. 28284.

⁵⁷ EPA. Biden-Harris Administration Proposes Ban on Trichloroethylene to Protect Public from Toxic Chemical Known to Cause Serious Health Risks. October 23, 2023. <https://www.epa.gov/newsreleases/biden-harris-administration-proposes-ban-trichloroethylene-protect-public-toxic> and 88 Fed. Reg. 74712.

⁵⁸ EPA. Integrated Risk Information System (IRIS) Glossary. Last updated 1/27/2023. https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do?sessionId=VYQEuB3zwOSBOnnxbuUp7aYNm18mPOKW8YvMXjY6P_kKAGKsVS5F!-1457352436?details=&vocabName=IRIS%20Glossary&filterTerm=Reference%20dose&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=Reference%20dose&filterMatchCriteria=Contains.

⁵⁹ EPA. IRIS. Benzene. Last updated 04/17/2003. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=276 .

Hematotoxicity and immunotoxicity have been consistently reported to be the most sensitive indicators of noncancer toxicity in both humans and experimental animals, and these effects have been the subject of several reviews ... The bone marrow is the target organ for the expression of benzene hematotoxicity and immunotoxicity. Leukocytopenia has been consistently shown to be a more sensitive indicator of benzene toxicity in experimental animal systems than anemia, and lymphocytopenia has been shown to be an even more sensitive indicator of benzene toxicity than overall leukocytopenia.” EPA assigns a “medium” confidence in the RfD.⁶⁰

- For methylene chloride (dichloromethane), the RfD of 0.006 mg/kg of body weight per day is based on hepatic (liver) effects (hepatic vacuolation, liver foci).⁶¹ EPA assigns a “high” confidence in the oral RfD.⁶²
- For trichloroethylene, the RfD of 0.0005 mg/kg of body weight per day is based on developmental and immune effects, including decreased thymus weight, developmental immunotoxicity, and fetal heart malformations.⁶³ EPA assigns a “high” confidence in the RfD.⁶⁴
- For ethylene dichloride, EPA has not established a RfD.⁶⁵ However, ATSDR has established a minimal risk level (MRL), which is similar to a reference dose. ATSDR defines an MRL as an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.⁶⁶ Unfortunately, ATSDR considered the data inadequate for deriving a chronic duration MRL because the most sensitive non-cancer endpoint was represented by a serious effect (death).⁶⁷ It did establish an intermediate-duration oral MRL of 0.2 mg/kg/day, based on increased kidney weight. Liver, body weight, cardiovascular, and hematological effects occurred at higher levels.

A 2023 article hypothesizes that trichloroethylene is an unrecognized cause of Parkinson’s Disease, citing animal evidence, case reports, and a small epidemiological study of twin pairs that found that the twin with occupational or hobby exposure to TCE had a 500% increased risk of Parkinson’s Disease (OR 6.1, 95% CI: 1.2-33, $p = 0.034$) compared to their unexposed twin.⁶⁸

The consumer, community, and occupational exposures that may result from the use of these solvents

⁶⁰ EPA. IRIS Chemical Assessment Summary. Benzene. Last revised 04/17/2003.

https://iris.epa.gov/static/pdfs/0276_summary.pdf.

⁶¹ EPA. IRIS. Dichloromethane. Last updated 11/18/2011.

https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=70.

⁶² EPA. IRIS. Chemical Assessment Summary. Dichloromethane. Last revised 11/18/2011.

https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0070_summary.pdf.

⁶³ EPA. IRIS. Trichloroethylene. Last updated 9/28/2011.

https://iris.epa.gov/ChemicalLanding/&substance_nmbr=199.

⁶⁴ EPA. IRIS. Chemical Assessment Summary. Trichloroethylene. Last revised 9/28/2011.

https://iris.epa.gov/static/pdfs/0199_summary.pdf.

⁶⁵ EPA. IRIS. 1,2-Dichloroethane. https://iris.epa.gov/ChemicalLanding/&substance_nmbr=149.

⁶⁶ ATSDR. Minimal Risk Levels (MRLs) for Hazardous Substances. Last reviewed 6/21/2018.

<https://www.atsdr.cdc.gov/mrls/index.html>.

⁶⁷ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comments. January 2022.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

⁶⁸ Dorsey ER, Zafar M, Lettenberger SE et al. Trichloroethylene: An Invisible Cause of Parkinson’s Disease? *J Parkinson’s Disease* 2023;13:203-218.

permitted by FDA are avoidable by using available alternatives.

IX. Conclusion

Based on the above conclusions by FDA, NTP, and other recognized authorities responsible for determining whether a substance is found to induce cancer in man or animal, FDA should remove its approvals for these chemicals when used as food additives because their uses are not safe pursuant to the Delaney Clause.

Appendix 1 of this petition summarizes the food additive regulations which currently reference these four chemicals, which authorities designated them as carcinogens, and when.

Appendix 2 provides additional details on the petition required by 21 CFR Part 171.1.

Appendix 3 supplies relevant reports on the carcinogenicity of benzene, ethylene dichloride, methylene chloride, and trichloroethylene.

Appendix 4 presents the specific changes we seek in the food additive regulations.

Appendix 5 is a numbered list of references (numbers used on file names) that corresponds to the files provided on the CD-ROM that accompanies the submission.

This letter, all appendices, and materials provided on a CD-ROM constitute our complete food additive petition. This petition contains no confidential information, so we ask that FDA include it in the docket for any regulatory action it takes so the public can assess the information.

If FDA grants this petition, it will have a positive impact on the environment, occupational health, and public health by reducing exposure to carcinogenic non-essential substances.

If you have questions or comments, please contact Tom Neltner, our agent on this petition, at tneltner@edf.org or 317-442-3973, and copy Lisa Lefferts at llefferts@earthlink.net on all responses.

Sincerely,



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Index to Appendices:

Appendix 1 Four Substances Permitted Under Food and Color Additive Regulations That Have Been Designated/Recognized as Carcinogenic by a Recognized Authority

Appendix 2 Responses to elements required by 21 CFR § 171.1

Appendix 3 Reports on the Carcinogenicity of Benzene, Ethylene Dichloride, Methylene Chloride, and Trichloroethylene

Part 1: Evaluations and Pronouncements by FDA

Part 2: Evaluations Organized by Other Recognized Authorities

Part 3: Evaluations by Other Recognized Authorities Organized by Additive

Part 4: Expanded Literature Search

Appendix 4 Requested Changes to Food Additive Regulations

Part 1: Requested changes to 21 CFR § 172.560

Part 2: Requested changes to 21 CFR § 172.7100

Part 3: Requested changes to 21 CFR § 173.230

Part 4: Requested changes to 21 CFR § 173.255

Part 5: Requested changes to 21 CFR § 173.290

Part 6: Requested changes to 21 CFR § 173.315(a)(4)

Appendix 5 List of References

Appendix 1
Four Substances Permitted Under Food Additive Regulations That
Have Been Designated/Recognized as Carcinogenic by a Recognized Authority

Additive name	CAS No.	Uses in Food*	Authority** and Year Designated as Carcinogenic (sorted with most recent first)
Benzene	71-43-2	<p>§ 172.560: Flavoring Agents and Related Substances – Modified hop extract. Used to manufacture modified hop extract from hops</p> <p>(Other uses not covered by this petition: Indirect additive uses in § 175.105 Adhesives)</p>	<p>FDA: Alert to Drug Manufacturers (known human carcinogen) (2022)†</p> <p>FDA: Class I Solvent: Carcinogen (2018)</p> <p>IARC: Carcinogenic to Humans (Group 1) (2018)</p> <p>ATSDR Tox Profile (2007) and Addendum (2015)</p> <p>NTP Study: Clear evidence in male haploinsufficient p16^{Ink4a}/p19^{Arf} mice (2007)</p> <p>EPA: Known Human Carcinogen (Category A) (2000)</p> <p>CA Prop 65 Carcinogen (1987)</p> <p>NTP Study: Clear Evidence (both species/sexes tested) (1986)</p> <p>HHS RoC: Known to be a Human Carcinogen (1980)</p>
Ethylene dichloride/1,2-Dichloroethane	107-06-2	<p>§ 172.560: Flavoring Agents and Related Substances – Modified hop extract; Used to manufacture modified hop extract from hops.</p> <p>§ 172.710 Adjuvants for pesticide use dilutions</p> <p>§ 173.230 Solvents, Lubricants, Release agents and Related Substances – Ethylene dichloride; Used to manufacture spice oleoresins.</p> <p>§ 173.315 Chemicals used in flume water for washing sugar beets prior to the slicing operation; ethylene dichloride is listed</p> <p>(Other uses not covered by this petition: Indirect uses in § 177.1580 (polycarbonate resins); § 573.440 (Ethylene dichloride is permitted to be used as a solvent in extraction processing of animal byproducts for use in animal feeds.))</p>	<p>ATSDR Tox Profile Draft for Public Comment (2022)</p> <p>IARC: Possibly Carcinogenic to Humans (Group 2B) (1999)</p> <p>CA Prop 65 Carcinogen (1987)</p> <p>EPA: Probable Human Carcinogen (Category B2) (1987)</p> <p>HHS RoC: Reasonably Anticipated to be a Human Carcinogen (1981)</p> <p>NTP Study: Carcinogenic – Positive (both species/sexes tested) (1978)</p>

Methylene chloride/ Dichloromethane	75-09-2	<p>§ 172.560: Flavoring Agents and Related Substances – Modified hop extract; Used to manufacture modified hop extract from hops</p> <p>§ 173.255 Solvents, Lubricants, Release Agents and Related Substances – may be present in spice oleoresins, hops extract, coffee, as a residue from the extraction of spice, hops, and caffeine from green coffee bean, respectively</p> <p>(Other uses not covered by this petition: Indirect additive uses in § 175.105 (Adhesives), § 177.1580 (polycarbonate resins))</p>	<p>EPA: Final Risk Evaluation (2020)</p> <p>IARC: Probably Carcinogenic to Humans (Group 2A) (2016)</p> <p>EPA: Likely to be Carcinogenic to Humans (2011)</p> <p>ATSDR Tox Profile (2000) and Systematic Evidence Map (2022)</p> <p>FDA: Ban on Use in Cosmetic Products (1989)</p> <p>CA Prop 65 Carcinogen (1988)</p> <p>HHS RoC: Reasonably Anticipated to be a Human Carcinogen (1989)</p> <p>NTP Study: Clear Evidence (female rats, male and female mice) (1986), Some Evidence (male rats)</p>
Trichloroethylene/ TCE	79-01-6	<p>§ 172.560: Flavoring Agents and Related Substances – Modified hop extract; Used to manufacture modified hop extract from hops</p> <p>§ 173.290 Solvents, Lubricants, Release agents and Related Substances –establishes tolerances in decaffeinated ground coffee, decaffeinated soluble (instant) coffee extract, and spice oleoresins resulting from its use as a solvent.</p>	<p>EPA: Final Revised Unreasonable Risk Determination (2023)</p> <p>ATSDR Tox Profile (2019)</p> <p>EPA: Carcinogenic to Humans (2011)</p> <p>HHS RoC: Known to be a Human Carcinogen (Initially listed as “Reasonably Anticipated to be a Human Carcinogen in 2000) and Monograph (2015)</p> <p>IARC: Carcinogenic to Humans (Group 1) (2014)</p> <p>CA Prop 65 Carcinogen (1988)</p> <p>NTP Study: Carcinogenic (mice (both sexes)); inadequate in male rats, no evidence in female rats (1990)</p> <p>NTP Study: Inadequate (1988)</p> <p>FDA: Proposed Rules to Remove Trichloroethylene due to tests finding it induces cancer (1977)</p> <p>NTP Study: Carcinogenic – Positive (mice (both sexes)); negative/inconclusive in rats (1976)</p>
<p>* Specifically:</p> <p>172: Food Additives Permitted for Direct Addition to Food For Human Consumption</p> <p>173: Secondary Direct Food Additives Permitted in Food for Human Consumption</p>			

** Abbreviations used:

ATSDR = Agency for Toxic Substances and Disease Registry

CAS = Chemical Abstracts Service

EPA = U.S. Environmental Protection Agency

FDA = U.S. Food and Drug Administration

HHS = U.S. Department of Health and Human Services

IARC = International Agency for Research on Cancer (part of WHO)

NTP = National Toxicology Program

RoC = Report on Carcinogens (prepared by NTP on behalf of the Secretary of Health and Human Services)

Tox Profile = Toxicological Profile (prepared by ATSDR)

† This is a public statement (alert) and not an assessment, but clearly states, “Benzene is a known human carcinogen that causes leukemia and other blood disorders,” and FDA would not have issued it without having ensured its accuracy based on a thorough assessment. It links to FDA guidance which also states that benzene is a carcinogen.

See next page for references.

Sources for Appendix 1:

Benzene

- a. FDA. FDA Alerts Drug Manufacturers to the Risk of Benzene Contamination in Certain Drugs. Content Current as of 12/23/2022. <https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs/>
- b. FDA: FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4> .
- c. FDA. Appendix 4: Toxicological Data for Class 1 Solvents. <https://www.fda.gov/media/71738/download>. Also available as ICH Guideline Q3C (R6) on Impurities – Support Document 1: Toxicological Data for Class I Solvents. European Medicines Agency, October 2018. at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.
- d. IARC. Benzene, IARC Monograph – Volume 120, 2018, p. 297. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Benzene-2018>.
- e. ATSDR. Toxicological Profile for Benzene. 2007. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.
- f. ATSDR. Addendum to the Toxicological Profile for Benzene. 2015. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.
- g. NTP. NTP Genetically Modified Model Report on the Toxicology and Carcinogenesis Studies of Benzene (CASRN 71-43-2) in Genetically Modified Haploinsufficient p16^{ink4a}/p19^{Arf} Mice (Gavage Study), NTP GMM 8, NIH Publication No. 08-4425, 2007. <https://ntp.niehs.nih.gov/publications/reports/gmm/gmm08>.
- h. EPA. Integrated Risk Information System (IRIS) Chemical Assessment Summary, Benzene (CAS No. 71-43-2). Carcinogenicity Assessment Last Revised 2000. https://iris.epa.gov/static/pdfs/0276_summary.pdf.
- i. OEHHA. Proposition 65. Benzene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/benzene>.
- j. NTP. Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No. 289, 1986. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr289.pdf.
- k. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Benzene, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/benzene.pdf>.

Ethylene Dichloride

- l. ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.
- m. IARC. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part 1, Part 2, Part 3) – Volume 71, 1999, p. 522. <https://publications.iarc.fr/89>. [Includes 1,2-Dichloroethane.]
- n. OEHHA. Proposition 65. Ethylene Dichloride (1,2-Dichloroethane). 2023. <https://oehha.ca.gov/proposition-65/chemicals/ethylene-dichloride-12-dichloroethane>.
- o. EPA. IRIS Chemical Assessment Summary, 1,2-Dichloroethane (CASRN 107-06-2). Carcinogenicity Assessment Last Revised 1987. https://iris.epa.gov/static/pdfs/0149_summary.pdf.
- p. HHS, NTP. Report on Carcinogens, Fifteenth Edition, 1,2-Dichloroethane, 2021. <https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/dichloroethane.pdf>.

- q. NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity (CAS No. 107-06-2), Technical Report Series No. 55, 1978.
<https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055/index.html>.

Methylene Chloride

- r. EPA. Final Risk Evaluation for Methylene Chloride. Last updated on April 20, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-methylene-chloride-0>.
- s. IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 243. [Includes methylene chloride.] <https://publications.iarc.fr/547>.
- t. EPA. IRIS Chemical Assessment Summary. Dichloromethane (CASRN 75-09-2). Carcinogenicity Assessment Last Revised 2011.
https://iris.epa.gov/static/pdfs/0070_summary.pdf.
- u. ATSDR Toxicological Profile for Methylene Chloride. 2000.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
- v. ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
- w. FDA. Cosmetics; Ban on the Use of Methylene Chloride as an Ingredient of Cosmetic Products. 54 Fed. Reg. 27328 (June 29, 1989), p. 27330.
- x. OEHHA. Proposition 65. Dichloromethane (Methylene Chloride), 2023. <https://oehha.ca.gov/proposition-65/chemicals/dichloromethane-methylene-chloride>.
- y. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Dichloromethane, 2021.
<https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloromethane.pdf>.
- z. NTP. Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Series No. 306, 1986.
<https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr306/index.html>.

Trichloroethylene

- aa. EPA. EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health. Released on January 9, 2023. <https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health>; Final Risk Evaluation for Trichloroethylene. Last updated on June 15, 2023.
<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-trichloroethylene>.
- bb. ATSDR. Toxicological Profile for Trichloroethylene. 2019.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.
- cc. EPA. IRIS Chemical Assessment Summary. Trichloroethylene (CASRN 79-01-6). Carcinogenicity Assessment Last Revised 2011.
https://iris.epa.gov/static/pdfs/0199_summary.pdf.
- dd. EPA. Toxicological Review of Trichloroethylene. EPA/635/R-09/011F, 2011.
https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf.
- ee. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Trichloroethylene, 2021.
<https://ntp.niehs.nih.gov/ntp/roc/content/profiles/trichloroethylene.pdf>.
- ff. HHS, NTP. Report on Carcinogens Monograph on Trichloroethylene. RoC Monograph 05. 2015.
https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/monographs/finaltce_508.pdf.
- gg. IARC. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated

- Agents. Volume 106. 2014. <https://publications.iarc.fr/130>
- hh. OEHHA. Proposition 65, Trichloroethylene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/trichloroethylene>.
- ii. NTP. Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No.243, 1990
<https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr243/index.html>.
- jj. NTP. Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies), Technical Report Series No.273, 1988.
<https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr273/index.html>.
- kk. FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).
- ll. FDA, Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene. 42 Fed. Reg. 49464 (September 27, 1977).
- mm. NTP. Carcinogenesis Bioassay of Trichloroethylene (CAS No. 79-01-6), Technical Report Series No. 2, 1976.
<https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr002/index.html>.

Appendix 2
Responses to elements required by 21 CFR § 171.1

A. Name and Pertinent Information Concerning Food Additive

The identity of the chemicals that appear in food additive regulations are as follows:

Additive name	Molecular formula	Molecular Weight (g/mol)	CAS No.	UNI No	Synonyms
Benzene	C ₆ H ₆	78.11	71-43-2	J64922108F	benzol; coal, naphtha; cyclohexatriene
Ethylene dichloride/1,2-Dichloroethane	C ₂ H ₄ Cl ₂	98.96	107-06-2	55163IJI47	1,2-dichloroethane; EDC; ethane, 1,2-dichloro; ethylene chloride; alpha, beta-dichloroethane
Methylene chloride/Dichloromethane		84.93	75-09-2	588X2YUY0 A	dichloromethane; methane, dichloro
Trichloroethylene/TCE	C ₂ HCl ₃	131.38	79-01-6	290YE8AR51	ethene, trichloro-; ethylene, trichloro-; Trichloroethene; 1,1,2-trichloroethylene

Sources:

- a. National Library of Medicine. PubChem. <https://pubchem.ncbi.nlm.nih.gov/>, specifically <https://pubchem.ncbi.nlm.nih.gov/compound/241>, <https://pubchem.ncbi.nlm.nih.gov/compound/11>, <https://pubchem.ncbi.nlm.nih.gov/compound/6344>, <https://pubchem.ncbi.nlm.nih.gov/compound/6575>.
- b. FDA. Substances Added to Food (formerly EAFUS). <https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus>, specifically https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances&id=BENZENE&sort=Sortterm_ID&order=ASC&startrow=1&type=basic&search=benzene, https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=ETHYLENEDICHLORIDE&sort=Sortterm_ID&order=ASC&startrow=1&type=basic&search=ethylene%20dichloride, <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=METHYLENECHLORIDE>, <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=TRICHLOROETHYLENE>.
- c. FDA. FDA's Global Substance Registration System. <https://precision.fda.gov/uniisearch>, specifically <https://precision.fda.gov/uniisearch/srs/unii/J64922108F>, <https://precision.fda.gov/uniisearch/srs/unii/55163IJI47>, <https://precision.fda.gov/uniisearch/srs/unii/588X2YUY0A>, <https://precision.fda.gov/uniisearch/srs/unii/290YE8AR51>.

B. Directions, Recommendations, and Suggestions Regarding Proposed Use

We are asking FDA to remove benzene, ethylene dichloride, methylene chloride, and trichloroethylene from Parts 172 and 173 of the food additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. We are not addressing their use as indirect additives or food contact substances at this time.

C. Data establishing that food additive will have intended physical or other technical effect

We are asking FDA to remove benzene, ethylene dichloride, methylene chloride, and trichloroethylene from Parts 172 and 173 of the food additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. We are not addressing their use as indirect additives or food contact substances at this time.

D. Description of practicable methods to determine the amount of the food additive in the food

We are asking FDA to remove benzene, ethylene dichloride, methylene chloride, and trichloroethylene from Parts 172 and 173 of the food additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. We are not addressing their use as indirect additives or food contact substances at this time.

If FDA no longer permits the use of these chemicals, there need be no practical methods to determine the amount added or remaining.

Nevertheless, since FDA currently specifies allowable residues of these chemicals in the food additive regulations, methods for their determination must currently be known to FDA. These include for benzene in modified hop extract; for ethylene dichloride in modified hop extract, spice oleoresins, and in flume water for washing beets; for methylene chloride in modified hops extract and spice oleoresins; and for methylene chloride and trichloroethylene in decaffeinated roasted coffee and instant coffee.

E. Full reports of investigations made with respect to the safety of the food additive.

See Appendix 3, as well as the cover letter portion of this petition.

F. Proposed tolerances for the food additive

We are asking FDA to remove benzene, ethylene dichloride, methylene chloride, and trichloroethylene from Parts 172 and 173 of the food additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. We are not addressing their use as indirect additives or food contact substances at this time.

As a result, no tolerance is needed, and none should be permitted.

G. Full information on each proposed change to the original regulation

See Appendix 4 for the specific changes requested to 21 CFR § 172.515. Text in strikethrough font is to be deleted.

H. Environmental review component

This food additive petition is categorically excluded from the need to prepare an Environmental Assessment under 21 C.F.R. § 25.32(m) as an “action to prohibit or otherwise restrict or reduce the use of a substance in food, food packaging, or cosmetics.” As the petitioned action is seeking revocation of the current authorizations of the use of benzene, ethylene dichloride, methylene chloride, and trichloroethylene in the food additive regulations as described in Section G and Appendix 4, this petition complies with the acceptance criteria of a claim of categorical exclusion under 21 C.F.R. § 25.32(m).

We have identified no extraordinary circumstances as defined at 21 C.F.R. § 25.21 for the action requested in this petition which would require the submission of an Environmental Assessment because the use of benzene, ethylene dichloride, methylene chloride, and trichloroethylene is not essential.

For each of the substances, we evaluated the alternatives more closely below:

1. Benzene

According to [§ 172.560](#), other substances including n-butyl alcohol and ethyl acetate can be used as solvents in the manufacture of modified hop extract from hops.

2. Ethylene dichloride

N-butyl alcohol and ethyl acetate can be used in the manufacture of modified hop extract from hops ([§ 172.560](#)).

Other adjuvants for pesticide use dilutions that are listed under [§172.710](#), can be used.

Acetone ([§ 173.210](#)) can be used for the extraction of spice and be present as a residue in spice oleoresins.

Numerous chemicals are permitted to be used in flume water for washing sugar beets prior to slicing operation under [§ 173.315](#); any of these could be used.

3. Methylene Chloride

Under [§ 173.228](#), ethyl acetate can be used in accordance with current good manufacturing practice as a solvent in the decaffeination of coffee and tea.

Although [§ 173.290](#) provides tolerances for trichloroethylene as a solvent in the manufacture of decaffeinated ground coffee and instant coffee extract, we exclude it as an alternative since it is a subject of this petition.

According to a chemical industry website ([ChemEurope](#)), a number of decaffeination methods are available in addition to methods that use methylene chloride, including methods using ethylene acetate; the Swiss water process, which uses only water as a solvent; supercritical fluid extraction, which uses carbon dioxide or oxygen; and the triglyceride process, which uses coffee oils obtained from spent coffee grounds. Methods using benzene (the Roselius process, no longer commercially used), or trichloroethylene, subjects of this petition, would not be acceptable.

4. Trichloroethylene

Under § [173.228](#), ethyl acetate can be used in accordance with current good manufacturing practice as a solvent in the decaffeination of coffee and tea.

Although § [173.255](#) provides tolerances for methylene chloride as a solvent for decaffeination, we exclude it as an alternative since it is a subject of this petition.

According to a chemical industry association ([ChemEurope](#)), a number of decaffeination methods are available in addition to methods that use methylene chloride (a subject of this petition) or ethylene acetate, including the Roselius process, which uses benzene (a subject of this petition) and is fortunately no longer authorized and thus would not be acceptable, the Swiss water process, which uses only water as a solvent, supercritical fluid extraction, which uses carbon dioxide, and the triglyceride process, which uses coffee oils obtained from spent coffee grounds.

Appendix 3

Reports on the Carcinogenicity of Benzene, Ethylene Dichloride, Methylene Chloride, and Trichloroethylene

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

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

We believe this finding should rest on conclusions already made by FDA and other recognized authorities responsible for determining whether a substance is found to induce cancer when ingested by man or animal.

We start by looking at FDA evaluations and pronouncements.

Part 1: Evaluations and Pronouncements by FDA

A. Benzene

FDA has worked with the beverage industry to minimize or eliminate benzene formation in beverage products, explaining that benzene is a concern because, “Benzene is a carcinogen that can cause cancer in humans.”⁶⁹ FDA has issued over a dozen drug recalls due to the presence of benzene,⁷⁰ and FDA urged consumers not to use any artnaturals™ hand sanitizers because it contained benzene and other contaminants, stating “Benzene may cause certain types of cancer in humans.”⁷¹ In its alert to drug manufacturers about the risk of benzene contamination in certain drugs, FDA states “Benzene is a known human carcinogen that causes leukemia and other blood disorders,” and “Manufacturers should not use benzene in the manufacture of drugs.”⁷² Yet, illogically, FDA approves the use of benzene in its food additive regulations, allowing manufacturers to use benzene in the manufacture of modified hop extract for use in food.

FDA considers benzene to be a “Class 1” solvent, meaning that it “should not be employed in the manufacture of drug substances, excipients, and drug products because of its unacceptable toxicity or

⁶⁹ FDA. Questions and Answers on the Occurrence of Benzene in Soft Drinks and Other Beverages. Content current as of 2/25/2022. <https://www.fda.gov/food/environmental-contaminants-food/questions-and-answers-occurrence-benzene-soft-drinks-and-other-beverages>.

⁷⁰ FDA. Drug Recalls. Content current as of June 14, 2023. <https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls>.

⁷¹ FDA. FDA Updates on Hand Sanitizers Consumers Should Not Use. 2021. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use>.

⁷² FDA. FDA Alerts Drug Manufacturers to the Risk of Benzene Contamination in Certain Drugs. Content current as of 12/23/2022. <https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs>.

deleterious environmental effect.”^{73,74} Specifically, for benzene, FDA identifies the concern as “carcinogen.”⁷⁵ A document entitled “Appendix 4: Toxicological Data for Class I Solvents” and also identified as a support document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) Guideline states:

“There is sufficient evidence to establish that benzene is a human carcinogen (lymphatic and hematopoietic cancers). In animal studies, Zymbal gland tumors, preputial gland tumors, skin carcinomas, mammary gland tumors and leukemia are observed.”⁷⁶

We note that the benzene entry in this document references IARC, ATSDR, and EPA, suggesting FDA's recognition that these agencies as authorities.

Currently, FDA is considering a citizen petition requesting the agency to recall identified batches of sunscreen products on the basis that, due to contamination with benzene, a known human carcinogen, these products are adulterated, to inform the public regarding these products, and to work with the U.S. EPA on a joint initiative to address benzene contamination, among other actions.⁷⁷

B. Ethylene Dichloride

FDA also identifies ethylene dichloride (1,2-dichloroethane) as a Class 1 solvent that should not be used to manufacture drugs.⁷⁸ The document entitled “Appendix 4: Toxicological Data for Class I Solvents,” and also identified as a support document for the International Council for Harmonisation of Technical Requirements for Pharmaceuticals (ICH) Guideline states under the heading “Carcinogenesis” that,

“There is no evidence of carcinogenicity in humans. Forestomach cancer, hemangiosarcoma, breast cancer, uterine cancer and respiratory cancer were found in rats or mice after gavage treatment.”⁷⁹

It also says, “possible human carcinogen (IARC 2B).” This entry references IARC and the 1978 NCI (now available through NTP⁸⁰) study.

⁷³ FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.

⁷⁴ FDA. Center for Drug Evaluation and Research. Office of Pharmaceutical Quality. Manual of Policies and Procedures. Acceptance Criteria for Residual Solvents. 2022. <https://www.fda.gov/media/75126/download>.

⁷⁵ FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.

⁷⁶ FDA. Appendix 4: Toxicological Data for Class 1 Solvents. <https://www.fda.gov/media/71738/download>. Also available as ICH Guideline Q3C (R6) on Impurities – Support Document 1: Toxicological Data for Class I Solvents. European Medicines Agency, October 2018. at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.

⁷⁷ Interim Response Letter from FDA to Valisure LLC dated November 19, 2021. <https://www.regulations.gov/document/FDA-2021-P-0497-0005>.

⁷⁸ FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.

⁷⁹ FDA. Appendix 4: Toxicological Data for Class 1 Solvents. <https://www.fda.gov/media/71738/download>. Also available at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.

⁸⁰ NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. TR-55, 1978. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055>.

C. Methylene Chloride

FDA described methylene chloride as “a carcinogenic chemical” in its 2003 final rule permitting the use of acesulfame potassium (it is a potential impurity of acesulfame potassium).⁸¹

In 1989, FDA deemed cosmetics containing methylene chloride as an ingredient to be adulterated and subject to regulatory action, based on an NTP study showing that inhalation of methylene chloride causes cancer in mice, and exposure estimates from its use in hair sprays.⁸² In its 1989 FDA final rule banning the use of methylene chloride as an ingredient of cosmetic products, based on the cancer evidence, FDA decided to separate the cosmetic and food additive issues and to defer any necessary action on the food additive uses of methylene chloride until a future date.⁸³ Over three decades have passed since then and FDA must now take action on the food additive uses of methylene chloride.

FDA justified its decision to defer action on the food additive uses of methylene chloride based in part on its determination that the potential carcinogenic risk from use of the additive for decaffeinating coffee was negligible. However, the Delaney Clause makes clear that FDA cannot consider a food additive or a color additive to be safe if it has been shown to induce cancer in animal studies.⁸⁴

FDA recognized this in its 2018 decision on synthetic flavoring agents, stating, “The Delaney Clause limits FDA’s discretion to determine the safety of food additives, in that it prevents FDA from finding a food additive to be safe if it has been found to induce cancer when ingested by humans or animals, regardless of the probability, or risk, of cancer associated with exposure to the additive or of the extent to which the experimental conditions of the animal study or the carcinogenic mode of action provide insight into the health effects of human consumption and use of the additive in question.”⁸⁵

In addition, FDA’s 1985 risk estimates are outdated. EPA’s cancer potency estimate updated in 2011 is five times greater than what FDA used in its 1985 estimate.⁸⁶ Also, FDA considered a “cup” of coffee to be 5 ounces; today, a “cup” of coffee at Starbucks ranges from 8 to 31 ounces.⁸⁷

We note that the oft-repeated claim^{88,89} that most companies engaged in decaffeination no longer use

⁸¹ FDA. Food Additives Permitted for Direct Addition to Food for Human Consumption: Acesulfame Potassium. 68 Fed. Reg. 75411 (December 31, 2003).

⁸² 21 CFR 700.19.

⁸³ FDA. Cosmetics; Ban on the Use of Methylene Chloride as an Ingredient of Cosmetic Products. 54 Fed. Reg. 27328 (June 29, 1989), p. 27330.

⁸⁴ Public Citizen v. Young, 831 F.2d 1108, 1122 (D.C. Cir. 1987); Les v. Reilly, 968 F.2d 985, 989 (9th Cir. 1992) (providing that “[t]hroughout its 30-year history, the Delaney clause has been interpreted as an absolute bar to all carcinogenic food additives” and that “. . . Congress has repeatedly ratified a strict interpretation of the Delaney clause” (internal citations omitted)).

⁸⁵ FDA. Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. 83 Fed Reg 50490 (October 9, 2018).

⁸⁶ According to EPA’s IRIS Chemical Assessment Summary last revised in 2011 (https://iris.epa.gov/static/pdfs/0070_summary.pdf), EPA’s potency estimate for methylene chloride is 2×10^{-3} per mg/kg-day. FDA used 4×10^{-4} per mg/kg-d in its risk estimate contained in 50 Fed. Reg. 51551 (December 18, 1985).

⁸⁷ Starbucks. What are the Sizes of Starbucks Drinks? 2022. <https://customerservice.starbucks.com/sbux?id=topics&article=KB0011498>.

⁸⁸ IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 182. <https://publications.iarc.fr/547>.

⁸⁹ ATSDR Toxicological Profile for Methylene Chloride. 2000. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

methylene chloride may not be true, at least not currently, given that methylene chloride was recently detected in ten popular brands of decaffeinated coffee, with some brands containing relatively high levels (e.g., up to 8.9 ppm).^{90,91}

D. Trichloroethylene

In 1977, FDA issued several proposed rules regarding trichloroethylene that were prompted by a bioassay by the NCI (now listed as an NTP report⁹²) that found that the chemical caused cancer in rodents. FDA states:

“The proposal to repeal the food additive use of trichloroethylene and this action [i.e., a proposal to amend the color additive regulations by deleting trichloroethylene from the list of permissible solvents in certain color additives] are based on the National Cancer Institute (NCI) report entitled “Carcinogenesis Bioassay of Trichloroethylene.” The report ... concludes that trichloroethylene induces liver cancer in mice. ... Elsewhere in this issue of the FEDERAL REGISTER, FDA is proposing (1) to amend the food additive regulations to delete provisions for use of trichloroethylene in the manufacture of foods and food contact surfaces; (2) to declare that any human or animal drug product containing trichloroethylene is a new drug or new animal drug and deemed to be misbranded; (3) to declare that any cosmetic product containing trichloroethylene is deemed to be adulterated; and (4) to declare that food or animal feed containing trichloroethylene is deemed to be adulterated. ... The Commissioner concludes that NCI’s report demonstrates that trichloroethylene is a carcinogen in test animals. Accordingly, under the provisions of section 706(b)(5)(B)(i) of the act, which is known as the Delaney clause (21 U.S.C. 376(b)(5)(B)(i)), its use in the production of a color additive may no longer be approved.”⁹³

In the proposed rule in 1977 pertaining to food additive uses, FDA proposed to revoke § 173.290 Trichloroethylene and to amend § 172.560 Modified hop extract, § 175.105 Adhesives, and § 177.1960 Vinyl chloride-hexene-1 copolymers by deleting the use of trichloroethylene currently permitted in those sections; and to amend Part 189 Substances Prohibited from Use in Human Food by adding two new sections for trichloroethylene.⁹⁴

In 1991, FDA withdrew these proposed rules, and many others as well, stating:

In many cases, these proposals have been superseded by subsequent actions or events or no longer reflect the agency’s regulatory objectives or priorities. In other cases, sufficient time has elapsed that it would be appropriate to publish a new proposal or tentative final rule before

⁹⁰ Clean Label Project. Are There Chemicals in Your Decaffeinated Coffee? 2023. <https://cleanlabelproject.org/are-there-chemicals-in-your-decaffeinated-coffee/>.

⁹¹ Clean Label Project. More Methylene Chloride!: The Most Common Solvent That is in Some of America’s Favorite Decaffeinated Coffees. 2023. https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper_3_2.pdf

⁹² NTP. Carcinogenesis Bioassay of Trichloroethylene. Technical Report 2. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr002>.

⁹³ FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene – Proposed Rule. 42 Fed. Reg. 49464 (September 27, 1977). <https://www.regulations.gov/document/FDA-1975-P-0006-0003>.

⁹⁴ FDA. Trichloroethylene: Removal from Food Additive Use – Notice of Proposed Rule Making. 42 FR 49465 (September 27, 1977). <https://www.regulations.gov/document/FDA-1976-N-0025-0001>.

proceeding to final action.⁹⁵

Thus, uses of trichloroethylene remain permitted.

In 2010, FDA implied that trichloroethylene is no longer being used in either the coffee or oleoresin industries.⁹⁶ No substantiation or documentation was provided. Verifying this information is difficult. Even if it were true in 2010, and remains true today, trichloroethylene's food-related uses remain legally permitted, and it could be used in the future.

⁹⁵ FDA. Withdrawal of Certain Pre-1986 Proposed Rules; Final Action. 56 Fed. Reg. 67440 (December 30, 1991). <https://www.regulations.gov/document/FDA-1975-P-0006-0005>.

⁹⁶ Letter from James C. Wallwork, Division of Petition Review, FDA Office of Food Additive Safety, to Sidney M. Wolfe, Director, Public Citizen Health Research Group, November 1, 2010. <https://www.regulations.gov/document/FDA-1975-P-0006-0008>.

Part 2: Evaluations Organized by Other Recognized Authorities

We incorporate the referenced findings of the recognized authorities by reference and summarize them below for each chemical.

A. U.S. Department of Health and Human Services Report on Carcinogens (Prepared by NTP)

Since 1978, Congress has directed the Secretary of the Department of Health and Human Services to publish a report, known as the Report on Carcinogens (ROC), identifying substances which either are known to be carcinogens or may reasonably be anticipated to be carcinogens, and to which a significant number of persons residing in the United States are exposed.^{97,98} NTP prepares the ROC on behalf of the Secretary. The most recent ROC is the fifteenth edition issued in December 2021.⁹⁹

The ROC designated **benzene** and **trichloroethylene** as “**known to be human carcinogen.**” This designation means:

“There is sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.”¹⁰⁰

The ROC designated **ethylene dichloride** and **methylene chloride**, as “**reasonably anticipated to be human carcinogen.**” This designation means either:

1. “There is limited evidence of carcinogenicity from studies in humans, which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded; or
2. There is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset; or
3. There is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.”¹⁰¹

⁹⁷ NTP. History of the Report on Carcinogens. <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/history>.

⁹⁸ 42 U.S.C. § 241.

⁹⁹ NTP. Fifteenth Report on Carcinogens, 2021. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc>.

¹⁰⁰ NTP. Fifteenth Report on Carcinogens, 2021, p. 6. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc> or https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/introduction_508.pdf.

¹⁰¹ NTP. Fifteenth Report on Carcinogens, 2021, p. 6. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc> or https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/introduction_508.pdf.

B. National Toxicology Program Cancer Studies

NTP was established in 1978 by the Secretary of HHS (then called the Department of Health, Education, and Welfare) and given permanent status in 1981 to test chemicals of public health concern, develop and validate new and better test methods, provide needed information to regulatory and research agencies, and strengthen the science base in toxicology.¹⁰² NTP is an interagency program composed of and supported by FDA's National Center for Toxicological Research (NCTR), the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health (NIH), and the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention (CDC).¹⁰³

According to NTP:

“Five categories of evidence of carcinogenic activity are used in the Technical Report series to summarize the strength of evidence observed in each experiment: two categories for positive results (clear evidence and some evidence); one category for uncertain findings (equivocal evidence); one category for no observable effects (no evidence); and one category for experiments that cannot be evaluated because of major flaws (inadequate study). These categories of interpretative conclusions were first adopted in June 1983 and then revised in March 1986 for use in the Technical Report series to incorporate more specifically the concept of actual weight of evidence of carcinogenic activity. For each separate experiment (male rats, female rats, male mice, female mice), one of the following five categories is selected to describe the findings. These categories refer to the strength of the experimental evidence and not to potency or mechanism.

Clear Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a dose-related (i) increase of malignant neoplasms, (ii) increase of a combination of malignant and benign neoplasms, or (iii) marked increase of benign neoplasms if there is an indication from this or other studies of the ability of such tumors to progress to malignancy.

Some Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a chemical-related increased incidence of neoplasms (malignant, benign, or combined) in which the strength of the response is less than that required for clear evidence.

Equivocal Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemically related.

No Evidence of Carcinogenic Activity is demonstrated by studies that are interpreted as showing no chemical-related increases in malignant or benign neoplasms.

Inadequate Study of Carcinogenic Activity is demonstrated by studies that because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.

... Earlier designations include P= Positive; E= Equivocal; N = Negative.”¹⁰⁴

NTP conducted cancer studies and published Technical Reports on all four chemicals. For each it

¹⁰² NTP. History & Milestones. <https://ntp.niehs.nih.gov/howeare/history>.

¹⁰³ NTP. Organization. <https://ntp.niehs.nih.gov/howeare/organization>.

¹⁰⁴ NTP. Cancer Evaluation Criteria. 2023. <https://ntp.niehs.nih.gov/whatwestudy/testpgm/cartox/criteria>.

found evidence of carcinogenicity. Each of NTP’s findings are discussed below in part 3 of this appendix. NTP made these findings pursuant to a Congressional directive at [42 U.S.C. § 241](#) to the HHS Secretary to conduct these types of tests. The Secretary established NTP to perform this work.

C. International Agency for Research on Cancer (IARC)

IARC is the specialized cancer agency of the World Health Organization (WHO) launched in 1965; through its Monographs program, IARC convenes international expert working groups that provide evaluations of evidence on the carcinogenicity of specific exposures.¹⁰⁵ The IARC Monographs have received funding from the U.S. NCI, the U.S. NIEHS, and the European Commission Directorate-General for Employment, Social Affairs, and Inclusion and other European agencies.¹⁰⁶ The most recent monograph was Volume 131 published in 2023.¹⁰⁷ Since it is part of WHO, we consider IARC to be a recognized authority, as as noted elsewhere in this petition, FDA has previously cited IARC’s determinations on carcinogenicity.

IARC designated **benzene** and **trichloroethylene** as “*carcinogenic to humans*” or **Group 1**. According to IARC:¹⁰⁸

“This category applies whenever there is *sufficient evidence of carcinogenicity* in humans.

In addition, this category may apply when there is both *strong evidence in exposed humans that the agent exhibits key characteristics of carcinogens* and *sufficient evidence of carcinogenicity* in experimental animals.”

IARC designated **methylene chloride** as “*probably carcinogenic to humans*” or **Group 2A**. According to IARC:¹⁰⁹

“This category generally applies when the Working Group has made at least *two of the following* evaluations, including at least one that involves either exposed humans or human cells or tissues:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,
- *Strong evidence that the agent exhibits key characteristics of carcinogens.*

If there is *inadequate evidence regarding carcinogenicity* in humans, there should be *strong evidence in human cells or tissues that the agent exhibits key characteristics of carcinogens*. If there is *limited evidence of carcinogenicity in humans*, then the second individual evaluation may be from experimental systems (i.e., *sufficient evidence of carcinogenicity* in experimental animals or *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens*).

Additional considerations apply when there is *strong evidence that the mechanism of*

¹⁰⁵ IARC. Mission. Accessed April 18, 2023, <https://www.iarc.who.int/iarc-mission/>.

¹⁰⁶ IARC. IARC Monographs – General Information. <https://monographs.iarc.who.int/home/iarc-monographs-general-information/>.

¹⁰⁷ IARC. Monographs available. <https://monographs.iarc.who.int/monographs-available/>.

¹⁰⁸ IARC, Preamble to the Monographs, p. 35, <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

¹⁰⁹ IARC, Preamble to the Monographs, p. 35, <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

carcinogenicity in experimental animals does not operate in humans for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of *sufficient evidence in experimental animals* in order for this evaluation to be used to support an overall classification in Group 2A.

Separately, this category generally applies if there is *strong evidence that the agent belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.*”

IARC designated ethylene dichloride as “**possibly carcinogenic to humans**” or **Group 2B**. According to IARC:¹¹⁰

“This category generally applies when only one of the following evaluations has been made by the Working Group:

- *Limited evidence of carcinogenicity* in humans,
- *Sufficient evidence of carcinogenicity* in experimental animals,
- *Strong evidence that the agent exhibits key characteristics of carcinogens.*

Because this category can be based on evidence from studies in experimental animals alone, there is **no** requirement that the strong mechanistic evidence be in exposed humans or in human cells or tissues. This category may be based on *strong evidence in experimental systems that the agent exhibits key characteristics of carcinogens.*

As with Group 2A, additional considerations apply when there is *strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans* for one or more tumour sites. Specifically, the remaining tumour sites should still support an evaluation of sufficient evidence in experimental animals in order for this evaluation to be used to support an overall classification in Group 2B.”

IARC has specific criteria defining what “*sufficient evidence of carcinogenicity*” and “*limited evidence of carcinogenicity*” means (defined both for human evidence, and separately for animal evidence), as well as criteria for “*strong evidence that the agent exhibits key characteristics of carcinogens.*”¹¹¹ Each of IARC’s findings are discussed below in part 3 of this appendix.

D. California’s Proposition 65 (California) OEHHA

The Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65, is a regulatory program that protects California’s drinking water sources from chemicals known to cause cancer, birth defects, or other reproductive harm, and requires businesses to provide warnings to Californians about exposures to such chemicals.¹¹² The Office of Environmental Health Hazard Assessment (OEHHA) administers Proposition 65. Through a process that includes public notice and an opportunity to comment, OEHHA has designated all four chemicals that are the subject of this

¹¹⁰ IARC, Preamble to the Monographs, p. 36, 2019. <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

¹¹¹ IARC, Preamble to the Monographs, p. 31-34, 2019. <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

¹¹² OEHHA, Proposition 65, 2023. <http://www.oehha.ca.gov/prop65.html>.

petition as carcinogens. A chemical is designated a **carcinogen** by one of four mechanisms^{113,114}:

1. **Labor Code.** Proposition 65 includes chemicals identified in California Labor Code section 6382(b)(1) or (d). Labor Code section 6382(b)(1) incorporates substances listed as human or animal carcinogens by IARC. Labor Code section 6382(d) refers to substances identified as carcinogens or potential carcinogens by IARC or NTP. This method established the initial chemical list following voter approval of Proposition 65 in 1986 and continues to be used as a basis for listing as appropriate. OEHHA designated **benzene** through this mechanism.
2. **State’s Qualified Experts.** An independent committee of scientific and health experts known as the Carcinogen Identification Committee (CIC) are “appointed by the Governor to identify chemicals that have been clearly shown through scientifically valid testing according to generally accepted principles to cause cancer,” and are designated as the “State’s Qualified Experts” for evaluating chemicals under Proposition 65.¹¹⁵ When determining whether a chemical should be placed on the list, the committees base their decisions on the most current scientific information available. OEHHA staff scientists compile all relevant scientific evidence on various chemicals for the committees to review. The committees also consider comments from the public before making their decisions. OEHHA designated **ethylene dichloride, methylene chloride (dichloromethane), and trichloroethylene** as carcinogens through this mechanism.
3. **Authoritative Bodies.** If an organization designated as an “authoritative body” by the CIC has identified a substance as causing cancer, it will be added to the Proposition 65 list. The following organizations have been designated as authoritative bodies: EPA, FDA, National Institute for Occupational Safety and Health, NTP, and IARC. Although authoritative bodies have determined all four chemicals to be carcinogenic, none were designated as carcinogens through this this mechanism.
4. **Formally Required to be Labeled.** A substance required by an agency of the state or federal government to be labeled or identified as causing cancer or birth defects or other reproductive harm, such as prescription drugs that are required by the U.S. FDA to contain warnings relating to cancer or birth defects or other reproductive harm, are added to the Proposition 65 list. None of the four chemicals were designated as carcinogens through this mechanism.

E. U.S. Environmental Protection Agency

EPA was established in 1970 by President Richard Nixon to protect human health and the environment.¹¹⁶ EPA’s Integrated Risk Information System (IRIS) program, located within EPA’s Center for Public Health and Environmental Assessment (CPHEA) in the Office of Research and Development (ORD) identifies and characterizes the health hazards of chemicals in the environment.¹¹⁷ EPA’s IRIS classified **benzene** as a “**known**” **human carcinogen**, **trichloroethylene** as “**carcinogenic to humans**”, **ethylene dichloride (1,2-dichloroethane)** as “**probable human carcinogen**” and **methylene chloride (dichloromethane)** as “**likely to be carcinogenic to humans.**” (The difference in terminology relates to the year the determination was made and the guidelines being used by IRIS at the time.) Each of EPA’s findings under IRIS are discussed below.

¹¹³ OEHHA, How chemicals are added to the Proposition 65 list, 2023. <https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list>.

¹¹⁴ OEHHA, Proposition 65 in Plain Language, 2023. <http://www.oehha.ca.gov/prop65/background/p65plain.html>.

¹¹⁵ OEHHA, Proposition 65, Carcinogen Identification Committee. Undated. <https://oehha.ca.gov/proposition-65/carcinogen-identification-committee>. Also see Cal. Health & Safety Code § 25249.8 .

¹¹⁶ EPA. EPA History. Last updated on April 17, 2023. <https://www.epa.gov/history>.

¹¹⁷ EPA. Basic Information about the Integrated Risk Information System. Last updated on May 18, 2023. <https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system>.

EPA also evaluates the risk of chemicals under TSCA to determine whether they present an unreasonable risk to public health or the environment under the conditions of use.¹¹⁸ EPA has completed risk evaluations for **trichloroethylene** and **methylene chloride** and determined that they pose unreasonable risks to human health, in part because of their cancer risks.¹¹⁹⁻¹²¹ Ethylene dichloride (1,2-dichloroethane) is currently undergoing risk evaluation, having been identified as a high priority chemical in December 2019.¹²²

After reviewing health effects data, EPA sets non-enforceable public health goals, called maximum contaminant level goals (MCLGs). An MCLG is “the maximum level of a contaminant in drinking water at which no known or anticipated adverse effect on health of persons would occur, allowing an adequate margin of safety.” For chemical contaminants that are carcinogens, EPA sets the MCLG at zero if there is evidence that a chemical may cause cancer, and there is no dose below which the chemical is considered safe.¹²³ EPA has set the MCLG at **zero** for **benzene**, **ethylene dichloride (1,2-dichloroethane)**, **methylene chloride (dichloromethane)**, and **trichloroethylene** at least in part because of an increased risk of cancer.¹²⁴

Hazardous air pollutants are those known to cause cancer and other serious health impacts.¹²⁵ **Benzene**, **ethylene dichloride (1,2-dichloroethane)**, **methylene chloride (dichloromethane)**, and **trichloroethylene** are listed by EPA as **hazardous air pollutants**.¹²⁶

EPA’s carcinogenicity findings for the four chemicals are discussed below in part 3 of this appendix.

F. Agency for Toxic Substances and Disease Registry Toxicological Profile

ATSDR, like FDA and NTP, is a federal public health agency of HHS. As part of its mission to protect communities from harmful health effects related to hazardous substances, ATSDR conducts comprehensive evaluations of toxicological information on specific substances and publishes the information as a Toxicological (Tox) Profile.¹²⁷ Each profile undergoes internal review and peer review, identifies and reviews the literature that describes a hazardous substance’s toxicologic properties, and describes the adequacy of information to determine a substance’s health effects.¹²⁸ ATSDR has completed

¹¹⁸ EPA. Risk Evaluations for Existing Chemicals under TSCA. Last updated February 24, 2023.

<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca>.

¹¹⁹ EPA. Chemicals Undergoing Risk Evaluation under TSCA. Last updated on June 8, 2023.

<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca>.

¹²⁰ EPA. EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health. Released on January 9, 2023.

<https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health>.

¹²¹ EPA. Nontechnical Summary of the Risk Evaluation for Methylene Chloride. June 2020.

https://19january2021snapshot.epa.gov/sites/static/files/2020-06/documents/mc_final_re_nontechnical_summary.pdf.

¹²² EPA. Risk Evaluation for 1,2-Dichloroethane. Last updated on May 25, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-12-dichloroethane>.

¹²³ EPA. How EPA Regulates Drinking Water Contaminants. Last Updated November 2, 2022.

<https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants>.

¹²⁴ EPA. National Primary Drinking Water Regulations. Last updated on January 9, 2023.

<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations>.

¹²⁵ EPA. Hazardous Air Pollutants. Last updated on February 9, 2023. <https://www.epa.gov/haps>.

¹²⁶ EPA. Initial List of Hazardous Air Pollutants with Modifications. Last updated on June 18, 2020.

https://19january2021snapshot.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications_.html

¹²⁷ ATSDR. <https://www.atsdr.cdc.gov/>. Last updated May 10, 2023.

¹²⁸ ATSDR. Toxicological Profile for Benzene. 2007.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.

Tox Profiles for benzene,¹²⁹ **methylene chloride,**¹³⁰ and **trichloroethylene,**¹³¹ and has issued a Tox Profile draft for public comment on **ethylene dichloride**¹³² which affirm the carcinogenicity of these substances. It also recently published a **Systematic Evidence Map for methylene chloride**¹³³ which provides an overview of new evidence published since the Tox Profile was published which continues to affirm the carcinogenicity of methylene chloride.

¹²⁹ ATSDR. Toxicological Profile for Benzene. 2007.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>. Also see ATSDR Addendum to the Toxicological Profile for Benzene. 2015. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.

¹³⁰ ATSDR Toxicological Profile for Methylene Chloride. 2000.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

¹³¹ ATSDR. Toxicological Profile for Trichloroethylene. 2019.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.

¹³² ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

¹³³ ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022, p. 8

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

Part 3: Evaluations by Other Recognized Authorities Organized by Additive

We incorporate the referenced findings of the recognized authorities by reference and summarize them below for each of the four additives.

A. Benzene

IARC has evaluated benzene six times, starting in 1974. Benzene has been designated as *carcinogenic to humans* (Group 1) since 1979. The most recent IARC evaluation was in 2018; IARC again designated benzene as “*carcinogenic to humans* (Group 1).” It stated:

“There is *sufficient* evidence in humans for the carcinogenicity of benzene. Benzene causes acute myeloid leukaemia in adults.

Positive associations have been observed for non-Hodgkin lymphoma, chronic lymphoid leukaemia, multiple myeloma, chronic myeloid leukaemia, acute myeloid leukaemia in children, and cancer of the lung.

A small minority of the Working Group considered that benzene also causes non-Hodgkin lymphoma. A separate small minority considered that a positive association was not observed for cancer of the lung.”¹³⁴

IARC also stated:

“There were 17 studies that reported on the effects of benzene inhalation in male and female mice. Several studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in mice exposed to benzene. ...

There were four oral administration (gavage) and two intraperitoneal studies of benzene in male and female mice. Some studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in mice exposed to benzene. ...

There were five studies of the carcinogenicity of benzene in rats: four oral administration studies (by gavage of males and females of different strains, i.e., Sprague-Dawley, Wistar, and F344) and one inhalation study in Sprague-Dawley rats (in pregnant females and their male and female offspring). All studies reported an increase in the incidence of one or more types of neoplasms (including tumours of the haematopoietic and lymphoid tissues) in rats exposed to benzene. ...

There were 12 studies that reported on neoplasms and preneoplastic effects induced by benzene (three whole-body inhalation, three oral administration (gavage), and six skin application studies) in one or both sexes of four different genetically modified mouse models of different genetic backgrounds. It was demonstrated that benzene induced cancer in different tissues (including tumours of the haematopoietic and lymphoid tissues) of genetically modified

¹³⁴ IARC. Benzene, IARC Monograph – Volume 120, 2018, p. 297. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Benzene-2018>.

mice, depending upon the route of exposure. ...”¹³⁵

Regarding the animal evidence, IARC concluded, “There is *sufficient evidence* in experimental animals for the carcinogenicity of benzene.”¹³⁶

It also concluded:

“A Group 1 evaluation was supported by mechanistic data demonstrating that benzene exhibits many of the key characteristics of carcinogens. In particular, there is *strong* evidence, including in exposed humans, that benzene: is metabolically activated to electrophilic metabolites; induces oxidative stress and associated oxidative DNA damage; is genotoxic, inducing DNA damage and chromosomal changes; is immunosuppressive; and causes haematotoxicity.”¹³⁷

In 2007, NTP published a Technical Report that notes that, “Benzene is considered a known human carcinogen by the NTP and a group one carcinogen by the International Agency for Research on Cancer.” The conclusion of the NTP Technical Report is:

“Under the conditions of this 27-week gavage study, there was *clear evidence of carcinogenic activity* of benzene in male haploinsufficient p16^{Ink4a}/p19^{Arf} mice based on the occurrence of malignant lymphoma. There was no evidence of carcinogenic activity of benzene in haploinsufficient p16Ink4a/p19Arf female mice administered 25, 50, 100, or 200 mg/kg.”¹³⁸

In 2007, ATSDR published a Toxicological Profile for benzene. The plain language “Public Health Statement” in the profile states,

“Long-term exposure to benzene can cause cancer of the blood-forming organs. This condition is called leukemia. Exposure to benzene has been associated with development of a particular type of leukemia called acute myeloid leukemia (AML). The Department of Health and Human Services has determined that benzene is a known carcinogen (can cause cancer). Both the International Agency for Cancer Research and the EPA have determined that benzene is carcinogenic to humans.”¹³⁹

In 2015, ATSDR published an Addendum to the Toxicological Profile for benzene, which provides a supplement of the scientific data published in the open peer-reviewed literature since the release of the 2007 profile. It discussed a more recent IARC monograph which reaffirmed its earlier designation that benzene is carcinogenic to humans, the NTP study of benzene in p16ink4a/p19Arf haploinsufficient mice, and reviewed epidemiology studies published since the IARC monograph. It also reviewed findings since the 2007 profile that “add to the present understanding of mechanisms of benzene

¹³⁵ IARC. Benzene, 2018, p9. 293-294. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Benzene-2018>

¹³⁶ IARC. Benzene, 2018, p. 297. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Benzene-2018>

¹³⁷ Ibid.

¹³⁸ NTP. NTP Genetically Modified Model Report on the Toxicology and Carcinogenesis Studies of Benzene (CASRN 71-43-2) in Genetically Modified Haploinsufficient p16ink4a/p19Arf Mice (Gavage Study), NTP GMM 8, NIH Publication No. 08-4425, 2007. <https://ntp.niehs.nih.gov/publications/reports/gmm/gmm08>.

¹³⁹ ATSDR. Toxicological Profile for Benzene. 2007, p. 6. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.

hematotoxicity and carcinogenicity.”¹⁴⁰

In 2000, EPA’s IRIS program reviewed benzene for carcinogenicity. The EPA IRIS report for benzene states:

“Benzene is classified as a "known" human carcinogen (Category A) under the Risk Assessment Guidelines of 1986. Under the proposed revised Carcinogen Risk Assessment Guidelines (U.S. EPA, 1996), benzene is characterized as a known human carcinogen for all routes of exposure based upon convincing human evidence as well as supporting evidence from animal studies.”¹⁴¹

In 1987, California’s OEHHA designated benzene as a carcinogen and listed it under Proposition 65 under the Labor Code mechanism.¹⁴²

In 1986, a NTP Technical Report concluded:

“Under the conditions of these 2-year gavage studies, there was *clear evidence of carcinogenicity* of benzene for male F344/N rats, for female F344/N rats, for male B6C3F1 mice, and for female B6C3F1 mice. For male rats, benzene caused increased incidences of Zymbal gland carcinomas, squamous cell papillomas and squamous cell carcinomas of the oral cavity, and squamous cell papillomas and squamous cell carcinomas of the skin. For female rats, benzene caused increased incidences of Zymbal gland carcinomas and squamous cell papillomas and squamous cell carcinomas of the oral cavity. For male mice, benzene caused increased incidences of Zymbal gland squamous cell carcinomas, malignant lymphomas, alveolarbronchiolar carcinomas and alveolarbronchiolar adenomas or carcinomas (combined), harderian gland adenomas, and squamous cell carcinomas of the preputial gland. For female mice, benzene caused increased incidences of malignant lymphomas, ovarian granulosa cell tumors, ovarian benign mixed tumors, carcinomas and carcinosarcomas of the mammary gland, alveolarbronchiolar adenomas, alveolarbronchiolar carcinomas, and Zymbal gland squamous cell carcinomas. Dose-related lymphocytopenia was observed for male and female F344/N rats and male and female B6C3F1 mice.”¹⁴³

Benzene is also listed in the current (fifteenth) U.S. Report on Carcinogens as “*known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans.” Benzene was first listed in 1980. The Report states, “Studies in experimental animals, including many published after benzene was listed in the *First Annual Report on Carcinogens*, have demonstrated that benzene causes cancer at numerous tissue sites in rodents.”¹⁴⁴

B. Ethylene Dichloride (1,2-Dichloroethane)

In 2022, ATSDR published a Toxicological Profile Draft for Public Comment that identified nine human and nine animal studies relevant to the carcinogenicity of ethylene dichloride. The document notes that HHS has determined the chemical may reasonably be anticipated to be a human carcinogen,

¹⁴⁰ ATSDR. Addendum to the Toxicological Profile for Benzene. 2015.

<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.

¹⁴¹ EPA. Integrated Risk Information System (IRIS) Chemical Assessment Summary, Benzene (CAS No. 71-43-2). Carcinogenicity Assessment Last Revised 2000. https://iris.epa.gov/static/pdfs/0276_summary.pdf.

¹⁴² OEHHA. Benzene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/benzene>.

¹⁴³ NTP. Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No. 289, 1986. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr289.pdf.

¹⁴⁴ HHS, NTP. Report on Carcinogens, Fifteenth Edition, Benzene, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/benzene.pdf>.

that IARC has placed it in Group 2B (possibly carcinogenic to humans), and that EPA has classified it as a Group B2 carcinogen (probable human carcinogen). It states:

Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity in humans, due to complicating co-exposures to various other chemicals. There have been mixed results in animal studies of tumor incidence after 1,2-dichloroethane exposure via inhalation, though the studies in mice and rats that failed to find 1,2-dichloroethane induced carcinogenic effects after chronic exposure had limitations that may explain the lack of these effects. A more recent study found a dose-dependent increase in benign and malignant tumors in rats of both sexes and female mice after chronic inhalation exposure to 1,2-dichloroethane. 1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, causing statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice. Other animal bioassays provide supportive or suggestive evidence for the carcinogenicity of 1,2-dichloroethane. One study showed compound-related lung papillomas following lifetime dermal exposure of female mice. Another study found an increase in bronchioloalveolar adenomas and adenocarcinomas in mice of both sexes after intermediate dermal exposure. Two additional studies found that pulmonary adenomas were induced in mice by intraperitoneal injection. ...

The positive and suggestive carcinogenicity results from animal bioassays (Nagano et al. 2006; NCI 1978; Stoner 1991; Suguro et al. 2017; Theiss et al. 1977; Van Duuren et al. 1979), along with data indicating that 1,2-dichloroethane and certain metabolites are mutagenic and capable of forming DNA adducts as discussed in the preceding section, provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well.”¹⁴⁵

IARC first reviewed ethylene dichloride (1,2-dichloroethane) in 1979, before the current classification system was adopted. The monograph states, “There is *sufficient evidence* that 1,2-dichloroethane is carcinogenic in mice and rats. In the absence of adequate data in humans, it is reasonable, for practical purposes, to regard 1,2-dichloroethane as if it presented a carcinogenic risk to humans.”¹⁴⁶

In 1999, IARC designated ethylene dichloride (1,2-dichloroethane) as “*possibly carcinogenic to humans* (2B)” It stated that:

“1,2-Dichloroethane was tested in one experiment in mice and in one in rats by oral administration. In mice, it produced benign and malignant tumours of the lung and malignant lymphomas in animals of each sex, hepatocellular carcinomas in males and mammary and uterine adenocarcinomas in females. In rats, it produced carcinomas of the forestomach in males, benign and malignant mammary tumours in females and haemangiosarcomas in animals of each sex. No increase in tumour incidence was found after inhalation exposure in two experiments in rats or in

¹⁴⁵ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022, pp. 9, 172. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

¹⁴⁶ IARC. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Halogenated Hydrocarbons. Volume 20, 1979, p. 442. <https://publications.iarc.fr/38>.

one experiment in mice, but these studies were considered to be inadequate. In two other inhalation studies, one in mice and one in rats, 1,2-dichloroethane increased the incidence of tumours at various sites including the liver, lung and mammary gland.”¹⁴⁷

IARC concluded that “There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dichloroethane.”¹⁴⁸

In 1987, California’s OEHHA designated ethylene dichloride as a carcinogen based on the analysis of its independent committee of cancer experts.¹⁴⁹

In 1987, EPA classified ethylene dichloride (1,2-dichloroethane) as B2 or probable human carcinogen, “based on the induction of several tumor types in rats and mice treated by gavage and lung papillomas in mice after topical application.”¹⁵⁰

Ethylene dichloride is also listed in the current (fifteenth) U.S. Report on Carcinogens as “*reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals.” Ethylene dichloride was first listed in 1981. The Report states, “Oral exposure to 1,2-dichloroethane caused tumors in mice and rats at several different tissue sites.”¹⁵¹

An NTP Technical Report published in 1978 on a bioassay of ethylene dichloride conducted by NCI reported “*Positive*” results in male and female mice and rats. It concluded:

“Under the conditions of this study, 1,2-dichloroethane was carcinogenic to Osborne-Mendel rats, causing squamous-cell carcinomas of the forestomach, hemangiosarcomas, and subcutaneous fibromas in male rats and causing mammary adenocarcinomas in female rats. This compound was also found to be carcinogenic to B6C3F1 mice, causing mammary adenocarcinomas and endometrial tumors in female mice, and causing alveolar/bronchiolar adenomas in mice of both sexes.”¹⁵²

C. Methylene Chloride

In 2022 EPA released a final revised risk determination for methylene chloride. This risk determination is based on methylene chloride as a whole substance, rather than on individual conditions of use. EPA determined that methylene chloride, as a whole chemical substance, presents an unreasonable risk to human health. EPA’s unreasonable risk determination for methylene chloride was driven by risks associated with manufacturing (domestic and import), processing (including processing as a reactant/intermediate, incorporation into a formulation or mixture, repackaging, recycling), industrial and commercial uses (including in adhesives, sealants, and caulks; as a solvent that becomes part of a formulation or mixture; as a processing aid; for plastic and rubber products manufacturing), and many other uses. In addition to identifying certain non-cancer adverse effects from exposure to methylene

¹⁴⁷ IARC. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part 1, Part 2, Part 3) – Volume 71, 1999, p. 522. <https://publications.iarc.fr/89>. [Includes 1,2-Dichloroethane.]

¹⁴⁸ Ibid.

¹⁴⁹ OEHHA. Ethylene dichloride (1,2-Dichloroethane). <https://oehha.ca.gov/proposition-65/chemicals/ethylene-dichloride-12-dichloroethane>.

¹⁵⁰ EPA. IRIS Chemical Assessment Summary, 1,2-Dichloroethane (CASRN 107-06-2). Carcinogenicity Assessment Last Revised 1987. https://iris.epa.gov/static/pdfs/0149_summary.pdf.

¹⁵¹ HHS, NTP. Report on Carcinogens, Fifteenth Edition, 1,2-Dichloroethane, 2021. <https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/dichloroethane.pdf>.

¹⁵² NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity (CAS No. 107-06-2), Technical Report Series No. 55, 1978. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055/index.html>.

chloride, EPA identified cancer from long-term exposure to methylene chloride.¹⁵³ The final risk evaluation includes a 2020 risk evaluation, which states:

There is sufficient evidence of methylene chloride carcinogenicity from animal studies. Methylene chloride produced tumors at multiple sites, in males and females, in rats and mice, by oral and inhalation exposure, and in multiple studies. The most prominent findings were significant increases in liver (hepatocellular adenoma/carcinoma) and lung (bronchoalveolar adenoma/carcinoma) tumor incidences in male and female B6C3F1 and Crj:BDF1 mice by inhalation exposure in two separate bioassays (Aiso et al., 2014a; NTP, 1986), liver tumors in male B6C3F1 mice exposed via drinking water (Serota et al., 1986b; Hazleton Laboratories, 1983), and mammary gland tumors (adenoma/fibroadenoma) in male and female F344/N and F344/DuCrj rats exposed by inhalation in two separate bioassays (Aiso et al., 2014a; NTP, 1986). Other findings potentially related to treatment included increases in liver tumors in male rats with inhalation exposure (Aiso et al., 2014a) and female rats with drinking water exposure (Serota et al., 1986a; Hazleton Laboratories, 1983); hemangiomas/hemangiosarcomas in male and female mice by inhalation exposure (Aiso et al., 2014a); mononuclear cell leukemia in female rats by inhalation exposure (Aiso et al., 2014a; NTP, 1986); mesotheliomas, subcutaneous fibromas/fibrosarcomas, and salivary gland sarcomas in male rats by inhalation exposure (Aiso et al., 2014a; NTP, 1986; Burek et al., 1984); and brain (glial cell) tumors in male and female rats by inhalation exposure (Nitschke et al., 1988a). ...

Based on the evidence, EPA believes that the cancer results in animal studies are relevant to humans. Reasons include the demonstration of mutagenicity in human cells without exogenous GSTT1 and detected GSTT1 activity in human cells, some of which is comparable to GSTT1 activity in mice.¹⁵⁴

IARC first evaluated methylene chloride (dichloromethane) in 1987, designating it as “*possibly carcinogenic to humans* (Group 2B)” based on sufficient evidence in animals.¹⁵⁵

In 2016, IARC designated methylene chloride as “*probably carcinogenic to humans* (Group 2A).” It stated:

“There is *limited evidence* in humans for the carcinogenicity of dichloromethane. Positive associations have been observed between exposure to dichloromethane and cancer of the biliary tract and non-Hodgkin lymphoma. ...

The overall evaluation of Group 2A was based on *sufficient evidence* in experimental animals and *limited evidence* in humans. In addition, a Group 2A evaluation was also supported by *sufficient evidence* in experimental animals, and the *strong evidence* that the metabolism of dichloromethane via GSTT1 leads to the formation of reactive metabolites, that GSTT1 activity is strongly associated with genotoxicity in vitro and in vivo, and that GSTT1-mediated metabolism of dichloromethane occurs in humans.”¹⁵⁶

¹⁵³ EPA. Final Risk Evaluation for Methylene Chloride. Last updated on April 20, 2023.

<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-methylene-chloride-0> .

¹⁵⁴ EPA. Risk Evaluation for Methylene Chloride (Dichloromethane, DCM). EPA Document# EPA-740-RI-8010, June 2020, pp. 290-293. https://www.epa.gov/sites/default/files/2020-06/documents/1_mecl_risk_evaluation_final.pdf.

¹⁵⁵ IARC. Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volume 1 to 42. 1987, p. 62, 194. <https://publications.iarc.fr/139>.

¹⁵⁶ IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 243. [Includes methylene chloride.] <https://publications.iarc.fr/547>.

The monograph describes six studies in mice and increased incidences of hepatocellular carcinoma, hepatocellular adenoma or carcinoma (combined), bronchiolo-alveolar carcinoma, haemangioma of the liver and of all organs (including the liver); seven studies in rats and increased incidences of fibroma of the subcutis, fibroma or fibrosarcoma of the subcutis, salivary gland sarcomas, and mammary gland adenomas, and a minimal increase (positive trend test) in hepatocellular adenomas and carcinomas (combined); and one study in Syrian hamsters in which there was an increased incidence of malignant lymphomas (females).¹⁵⁷

In 2011, EPA designated methylene chloride as “likely to be carcinogenic in humans” following its 2005 Guidelines for Carcinogen Risk Assessment. It stated that this designation was based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays by NTP in male and female B6C3F1 mice (liver and lung tumors) with inhalation exposure, and at one site in male B6C3F1 mice with drinking water exposure, although there was additional evidence in rats that provided supporting evidence of carcinogenicity. Studies in humans linking occupational exposure to methylene chloride and some specific cancers (brain, liver and biliary tract, non-Hodgkin lymphoma, and multiple myeloma) were also reviewed.¹⁵⁸

In 2000, ATSDR published a Tox Profile on methylene chloride which reviews the cancer evidence. It states, “Inhalation studies in animals show a concentration-dependent, statistically significant increase in liver and lung adenomas and carcinomas in mice exposed to high concentration of methylene chloride (Mennear et al. 1988; NTP 1986) and benign mammary gland tumors in rats (Mennear et al. 1988; NTP 1986) following 2 years of exposure to methylene chloride. The evidence for carcinogenicity in animals from oral exposures (Serota et al. 1986a, 1986b) is inconclusive, and there are no dermal data available. Therefore, additional chronic oral and dermal studies are needed to clarify the cancer risk of ingested methylene chloride.”¹⁵⁹

In 2022 ATSDR published a Systematic Evidence Map for Methylene Chloride which contains updated information published since release of the Tox Profile. It states, “While evidence from human studies is mixed, findings from animal studies are consistent with the existing toxicological profile for methylene chloride (ATSDR 2000), indicating that the nervous system, liver, and kidney are potential toxicity targets of methylene chloride. Additional studies in animals also reported carcinogenic effects.”¹⁶⁰

We identified one additional cancer bioassay on methylene chloride in the 2022 ATSDR document: a 2014 study from the Japan Bioassay Research Center which states,

“Inhalation of DCM resulted in increased incidences of subcutis fibromas, mammary gland fibroadenoma, and peritoneum mesotheliomas in male rats; mammary gland fibroadenomas in female rats; and bronchiolar–alveolar adenomas and carcinomas in the lung and hepatocellular adenomas and carcinomas in male and female mice. These results clearly indicate that inhaled DCM is carcinogenic in F344/DuCrj (SPF) rats and Crj: BDF1 (SPF) mice.”¹⁶¹

¹⁵⁷ Ibid.

¹⁵⁸ EPA. IRIS Chemical Assessment Summary. Dichloromethane (CASRN 75-09-2). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0070_summary.pdf.

¹⁵⁹ ATSDR Toxicological Profile for Methylene Chloride. 2000, p. 153. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

¹⁶⁰ ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022, p. 8 <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

¹⁶¹ Aiso S, Take M, Kasai T, et al. Inhalation carcinogenicity of dichloromethane in rats and mice. *Inhal Toxicol* 2014;26(8):435-451. <https://doi.org/10.3109/08958378.2014.905660>.

The 2022 ATSDR document also identified a 1994 NTP technical report that compared the effects of different gavage vehicles in altering cancer rates in male F344/N rats, but the data were inadequate for assessing carcinogenicity of methylene chloride. The NTP report included a section on a 2-year study using methylene chloride, but it only used a single dose of methylene chloride, a single sex of a single species, and was done for a different purpose other than assessing the carcinogenic hazard of methylene chloride. Dichloromethane was used since it appears to cause pancreatic proliferative lesions when administered by gavage in corn oil, but not by inhalation, and control male rats receiving a corn oil vehicle have a higher incidence of pancreatic proliferative lesions than untreated control males. The study found that there were significantly increased incidences of benign pituitary tumors (pituitary gland distalis adenoma) in rats receiving methylene chloride in corn oil compared to those receiving comparable volumes of corn oil alone. The incidence of pituitary carcinoma was 3/50 in rats receiving methylene chloride in 10 ml corn oil compared to 0/50 in rats receiving 10 ml corn oil alone, but there was no difference in the incidence of pituitary carcinoma in treated rats receiving lower amounts of corn oil compared to those receiving comparable volumes of corn oil alone.¹⁶²

In 1988, California's OEHHA designated methylene chloride as a carcinogen based on the analysis of its independent committee of cancer experts.¹⁶³

Methylene chloride is currently listed in the Report on Carcinogens as "*reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals." Regarding cancer studies in experimental animals it said "Exposure to dichloromethane by inhalation caused tumors in two rodent species and at several different tissue sites. In mice of both sexes, it caused tumors of the lung (alveolar/bronchiolar tumors) and liver (hepatocellular tumors), and in rats of both sexes, it caused benign mammary-gland tumors (fibroadenoma) (NTP 1986)." It was first listed in 1989.¹⁶⁴

In a 1986 Technical Report, NTP stated:

"Under the conditions of these inhalation studies, there was *some evidence* of carcinogenicity of dichloromethane for male F344/N rats as shown by an increased incidence of benign neoplasms of the mammary gland. There was *clear evidence* of carcinogenicity of dichloromethane for female F344/N rats as shown by increased incidences of benign neoplasms of the mammary gland. There was *clear evidence* of carcinogenicity of dichloromethane for male and female B6C3F1 mice, as shown by increased incidences of alveolar/bronchiolar neoplasms and of hepatocellular neoplasms."¹⁶⁵

D. Trichloroethylene (TCE)

In 2023, EPA published its Final Revised Unreasonable Risk Determination for trichloroethylene, finding that it presents an unreasonable risk of injury to human health as a whole chemical substance. In addition

¹⁶² NTP. Technical Report Series No. 426. Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin in Male F344/N Rats As Vehicles for Gavage. 1994.

<https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr426>.

¹⁶³ OEHHA. Dichloromethane (Methylene Chloride). <https://oehha.ca.gov/proposition-65/chemicals/dichloromethane-methylene-chloride>.

¹⁶⁴ HHS, NTP. Report on Carcinogens, Fifteenth Edition, Dichloromethane, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloromethane.pdf>.

¹⁶⁵ NTP. Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Series No. 306, 1986. <https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr306/index.html>.

to identifying non-cancer risks, EPA identified risks for cancer.¹⁶⁶ It states, “Consistent with EPA guidance, in this Risk Evaluation EPA concluded that **TCE is carcinogenic** to workers and ONUs [occupational non-users] by all routes of exposure. This is most strongly supported by the data on kidney cancer.”¹⁶⁷

EPA determined that 52 out of 54 conditions of use evaluated would drive the determination that TCE presents an unreasonable risk of injury to human health. These include manufacturing (domestic and import), processing (including processing as a reactant/intermediate, incorporation into a formulation or mixture, incorporation into articles), industrial and commercial use as a precipitant used in the manufacture of beta-cyclodextrin (a flavoring substance), “miscellaneous industrial and commercial uses,” and many other uses.¹⁶⁸ The final risk evaluation includes a 2020 risk evaluation, which states:

“For this Risk Evaluation, EPA performed new meta-analyses incorporating both the initial group of studies assessed in the 2011 EPA TCE IRIS Assessment and any newer, on-topic studies of Acceptable data quality identified in the literature ... In summary, meta-analyses accounting for between-study heterogeneity, influential observations, and data quality consistently indicate positive associations of NHL, kidney cancer and liver cancer with exposure to TCE. This conclusion generally agrees with that of other governmental and international organizations. The International Agency for Research on Cancer (IARC) (IARC, 2014) found sufficient evidence for the carcinogenicity of TCE in humans. IARC definitively stated that TCE causes kidney cancer and determined that a positive association has been identified for NHL and liver cancer. Based on the weight of evidence when accounting for both these authoritative assessments and the results of EPA’s meta-analyses and in accordance with EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), **EPA determines that TCE is “Carcinogenic to Humans”**. Cancer was therefore carried forward for dose-response analysis, incorporating extra cancer risk from all three cancer types.”¹⁶⁹

In 2019, ATSDR published a Tox Profile which reviews the cancer evidence. It states:

“There is strong evidence that trichloroethylene can cause kidney cancer in people and some evidence that it causes liver cancer and malignant lymphoma (a blood cancer). Lifetime exposure to trichloroethylene resulted in increased liver cancer in mice and increased kidney cancer in rats at relatively high exposure levels. There is some evidence for trichloroethylene-induced testicular cancer and leukemia in rats and lymphomas and lung tumors in mice.

The Department of Human Health Services (HHS) has classified trichloroethylene as “known to be a human carcinogen” based on sufficient evidence of carcinogenicity from humans. Similarly, the International Agency for Research on Cancer (IARC) has classified it as “carcinogenic to humans” and EPA has characterized it as “carcinogenic in humans by all routes of exposure.” These agencies concluded that there was sufficient evidence from human studies that trichloroethylene exposure can cause kidney cancer in humans. There is also some evidence of an association

¹⁶⁶ EPA. EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health. Released on January 9, 2023. <https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health>; Final Risk Evaluation for Trichloroethylene. Last updated on June 15, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-trichloroethylene>.

¹⁶⁷ EPA. Final Risk Evaluation for Trichloroethylene. December 2022. P. 8. https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf.

¹⁶⁸ Ibid

¹⁶⁹ EPA, Risk Evaluation for Trichloroethylene, EPA Document #740R18008, 2020, pp. 251-252. https://www.epa.gov/sites/default/files/2020-11/documents/1_risk_evaluation_for_trichloroethylene_tce_casm_79-01-6.pdf.

between trichloroethylene exposure and non-Hodgkin's lymphoma in humans.”¹⁷⁰

In 2011, EPA's IRIS program characterized trichloroethylene as

“**Carcinogenic to humans**” by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The kidney cancer association cannot be reasonably attributed to chance, bias, or confounding. The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for non-Hodgkin lymphoma (NHL), but less convincing than for kidney cancer, and more limited for liver and biliary tract cancer. In addition to the body of evidence pertaining to kidney cancer, NHL, and liver cancer, the available epidemiologic studies also provide more limited evidence of an association between TCE exposure and other types of cancer, including bladder, esophageal, prostate, cervical, breast, and childhood leukemia. Differences between these sets of data and the data for kidney cancer, NHL, and liver cancer are observations from fewer numbers of studies, a mixed pattern of observed risk estimates, and the general absence of exposure-response data from the studies using a quantitative TCE-specific exposure measure.

There are several lines of supporting evidence for TCE carcinogenicity in humans. First, TCE induces multiple types of cancer in rodents given TCE by gavage and inhalation, including cancers in the same target tissues identified in the epidemiologic studies – kidney, liver, and lymphoid tissues. Second, toxicokinetic data indicate that TCE absorption, distribution, metabolism, and excretion are qualitatively similar in humans and rodents. Finally, there is sufficient weight of evidence to conclude that a mutagenic mode of action is operative for TCE-induced kidney tumors, and this mode of action is clearly relevant to humans. Modes of action have not been established for other TCE-induced cancers in rodents, and no mechanistic data indicate that any hypothesized key events are biologically precluded in humans.”¹⁷¹

Trichloroethylene is also listed in the current (fifteenth) U.S. Report on Carcinogens as:

“*known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on epidemiological studies showing that it causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans. Epidemiological studies also provide limited evidence that trichloroethylene causes non-Hodgkin lymphoma (NHL) in humans. Supporting evidence is provided by studies in experimental animals demonstrating that trichloroethylene causes cancer at several tissue sites, including some of the same sites as seen in humans.”¹⁷²

It was first listed in 2000.¹⁷³

In 2015, NTP published a Report on Carcinogens Monograph on trichloroethylene which it described as follows:

¹⁷⁰ATSDR. Toxicological Profile for Trichloroethylene. 2019, p. 4.

<https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.

¹⁷¹ EPA. IRIS Chemical Assessment Summary. Trichloroethylene (CASRN 79-01-6). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0199_summary.pdf.

¹⁷² HHS, NTP. Report on Carcinogens, Fifteenth Edition, Trichloroethylene, 2021.

<https://ntp.niehs.nih.gov/ntp/roc/content/profiles/trichloroethylene.pdf>.

¹⁷³ Ibid.

“The National Toxicology Program (NTP) conducted a cancer hazard assessment of TCE, focusing on three types of cancer kidney cancer, non-Hodgkin lymphoma (NHL), and liver cancer. NTP used systematic review methods to identify studies, evaluate study quality, integrate evidence across studies, and integrate evidence across data streams (human, animal, and mechanistic data). Using established criteria, NTP reached conclusions regarding the strength of the evidence for each of the three cancer types and on the recommended listing status of trichloroethylene in the Report on Carcinogens.”¹⁷⁴

It concluded:

“The NTP cancer hazard evaluation was the basis for changing the listing status of TCE from reasonably anticipated to known to be a human carcinogen in the 14th edition of the Report on Carcinogens based on sufficient evidence of carcinogenicity from studies in humans. This conclusion is based on epidemiological studies showing that TCE causes kidney cancer in humans, together with supporting evidence from toxicological, toxicokinetic, and mechanistic studies demonstrating the biological plausibility of its carcinogenicity in humans.”¹⁷⁵

IARC first considered trichloroethylene in 1976, prior to the current classification system. No human data were available at that time, but the 1976 monograph states, “According to a preliminary report, trichloroethylene induced liver-cell carcinomas in mice but not in rats after its oral administration.”¹⁷⁶ In 1979 IARC concluded, “There is *limited evidence* that trichloroethylene is carcinogenic in mice.”¹⁷⁷

In 2014 IARC designated trichloroethylene as “*carcinogenic to humans (Group 1)*.” It stated:

“There is *sufficient evidence* in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney. A positive association has been observed between exposure to trichloroethylene and non-Hodgkin lymphoma and liver cancer...

There is *sufficient evidence* in experimental animals for the carcinogenicity of trichloroethylene...

The Working Group was unanimous in its conclusion that trichloroethylene is a Group 1 carcinogen.”¹⁷⁸

In 1988, California’s OEHHA designated trichloroethylene as a carcinogen based on the analysis of its independent committee of cancer experts.¹⁷⁹

A 1990 NTP Technical Report found TCE (that was free of epichlorohydrin) to be carcinogenic in mice. It was conducted since the interpretation of an earlier NTP study in 1976 was complicated by the

¹⁷⁴ HHS, NTP. Report on Carcinogens Monograph on Trichloroethylene. RoC Monograph 05. 2015. https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/monographs/finaltce_508.pdf.

¹⁷⁵ Ibid.

¹⁷⁶ IARC. Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. Volume 11, 1976. P. 271. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Cadmium-Nickel-Some-Epoxides-Miscellaneous-Industrial-Chemicals-And-General-Considerations-On-Volatile-Anaesthetics-1976>.

¹⁷⁷ IARC. Some Halogenated Hydrocarbons. Volume 20, p. 561. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Halogenated-Hydrocarbons-1979>.

¹⁷⁸ IARC. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. Volume 106. 2014. <https://publications.iarc.fr/130>.

¹⁷⁹ OEHHA. Trichloroethylene. <https://oehha.ca.gov/proposition-65/chemicals/trichloroethylene>.

presence of epichlorohydrin (0.09%) in the test material. The report states:

“Under the conditions of these studies, epichlorohydrin-free trichloroethylene caused renal tubular-cell neoplasms in male F344/N rats, produced toxic nephrosis in both sexes, and shortened the survival time of males. This experiment in male F344/N rats was considered to be inadequate to evaluate the presence or absence of a carcinogenic response to trichloroethylene. For female F344/N rats receiving trichloroethylene, containing no epichlorohydrin, there was no evidence of carcinogenicity. Trichloroethylene (without epichlorohydrin) was carcinogenic for B6C3F1 mice, causing increased incidences of hepatocellular carcinomas in males and females and of hepatocellular adenomas in females.”¹⁸⁰

A 1988 NTP Technical Report was deemed “inadequate,” meaning that “because of major qualitative or quantitative limitations cannot be interpreted as valid for showing either the presence or absence of carcinogenic activity.” It concluded:

“Under the conditions of these 2-year gavage studies of trichloroethylene in male and female ACI, August, Marshall, and Osborne-Mendel rats, trichloroethylene administration caused renal tubular cell cytomegaly and toxic nephropathy in both sexes of the four strains. However, these are considered to be *inadequate studies of carcinogenic activity* because of chemically induced toxicity, reduced survival, and deficiencies in the conduct of the studies. Despite these limitations, tubular cell neoplasms of the kidney were observed in rats exposed to trichloroethylene and interstitial cell neoplasms of the testis were observed in Marshall rats exposed to trichloroethylene.”¹⁸¹

There was also a NTP Technical Report published in 1976 that reported “positive” results in mice (both sexes). It found negative/inconclusive results in rats. The report states:

“The results of this carcinogenesis test of trichloroethylene clearly indicate that trichloroethylene induced a hepatocellular carcinoma response in mice. While the absence of a similar effect in rats appears most likely attributable to a difference in sensitivity between the Osborne-Mendel rat and the B6C3F1 mouse, the early mortality of rats due to toxicity must also be considered.”¹⁸²

¹⁸⁰NTP. Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No.243, 1990
<https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr243/index.html>.

¹⁸¹ NTP. Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies), Technical Report Series No.273, 1988.
<https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr273/index.html>.

¹⁸² NTP. Carcinogenesis Bioassay of Trichloroethylene (CAS No. 79-01-6), Technical Report Series No. 2, 1976.
<https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr002/index.html>.

Part 4: Expanded Literature Search

For each of the four chemicals, we conducted an updated literature search for studies conducted from just prior to the most recent authoritative body review of evidence, until June 1, 2023.

Specifically:

- Benzene: 12/1/2022 – 6/1/2023, since FDA’s Alert to drug manufacturers to the risk of benzene contamination is current as of 12/23/2022;¹⁸³
- Ethylene Dichloride: 12/1/2021– 6/1/2023, since the ATSDR Tox Profile Draft for Public Comment was published January 2022;
- Methylene Chloride: 9/1/2022 – 6/1/2023, since the ATSDR Systematic Evidence Map was published October 2022;
- Trichloroethylene: 10/1/2020 – 6/1/2023, since the EPA Final Risk Evaluation was published November 2020.

We searched the following databases: PubMed and Web of Science.

We did not include the reports from OEHHA, IARC, EPA, or ATSDR described in the previous section.

The search included the following terms:

- Chemical names: benzene, ethylene dichloride, 1,2-dichloroethane, methylene chloride, dichloromethane, trichloroethylene, TCE, ethylene trichloride
- CAS Register numbers: 71-43-2, 107-06-2, 75-09-2, 79-01-6
- Cancer-related terms: cancer, carcinogenesis, carcinogenic, mutagenicity, mutagenic, genotoxicity, gene toxicity, DNA damage, DNA adducts

The cancer-related terms are the same as those used for the petition on carcinogenic flavors.¹⁸⁴

For benzene, the MeSH term was used in PubMed to exclude/cut down on other chemicals that contain the word benzene but are not the chemical of interest. Similarly, in Web of Science, the benzene search was run in the Web of Science Core Collection using all fields for all terms except for benzene where the Keyword Plus field and separately the Title field were applied, to produce a better-focused search. In addition, we ran another search on benzene using all fields for all terms and keyed to journals obtained from the previous Web of Science search, to ensure that no articles were missed.

We excluded results that were not about whether the substance could cause or promote cancer.

Studies are organized by year and alphabetized within each year, with most recent years listed first.

¹⁸³ FDA’s alert at <https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs> states, “Benzene is a known human carcinogen that causes leukemia and other blood disorders” and “Content current as of: 12/23/2022.” It does not contain a review or assessment of the evidence, but certainly had to have been based on one for FDA to issue it. It links to FDA’s guidance for Industry: Q3C Tables and List that also identifies benzene as a carcinogen, at <https://www.fda.gov/media/133650/download>.

¹⁸⁴ FDA, Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. 83 Fed. Reg. 50490 (October 9, 2018).

Summary of Results of Expanded Literature Search	
Additive name	Results
Benzene	4 additional human studies, no additional animal studies, 7 additional mechanistic studies, 5 additional reviews found. All reinforce the conclusion that benzene is carcinogenic.
Ethylene Dichloride	No additional studies found.
Methylene Chloride	One additional human study found, which reinforces the conclusion that methylene chloride is carcinogenic.
Trichloroethylene (TCE)	9 additional human studies, 2 additional animal studies, 3 additional mechanistic studies, 6 additional reviews found. One review neither reinforces nor refutes the conclusion that TCE is carcinogenic (it looked specifically at multiple myeloma and found no association with TCE). All the others found reinforce the conclusion that TCE is carcinogenic.

A. Benzene:

We found four human studies, seven genotoxicity and mechanistic studies, and five reviews on the ability of benzene to cause or promote cancer. We briefly describe each study or review below.

As might be expected for a chemical that has been known to cause cancer in humans for over 40 years, no studies in the recent literature dispute or contradict the universally held and amply documented assertion that benzene is carcinogenic. Indeed, they all reinforce, support, are consistent with, or extend the evidence for carcinogenicity of benzene, and/or provide clues about the mechanisms underlying benzene-induced carcinogenesis.

1. Human studies

- a. *Boyle J, Ward MH, Cerhan JR et al. Modeling Historic Environmental Pollutant Exposures and Non-Hodgkin Lymphoma Risk. Environ Res 2023;224:115506.*

This study examined associations between non-Hodgkin lymphoma (NHL) and historic environmental pollutant emissions from the Risk Screening Environmental Indicators (RSEI) model, which uses an EPA database of toxic release emissions to air, water, and land. (It also looked at the association between NHL and chemical mixtures measured in house dust, but these did not include any of the solvents subject to this petition.)

Participants were enrolled in the NCI Surveillance, Epidemiology, and End Results (SEER) population-based case-control study (1998-2000) at four SEER centers: Detroit, Iowa, Los Angeles County, and Seattle, and included 1,321 cases of NHL aged 20-74 years who were diagnosed between July 1, 1998 and June 30, 2000 and 1,057 population-based controls matched to cases by age within 5-year groups, sex, race, and study center. Researchers “found a significant positive association between RSEI scores and NHL at the maximum time lag of 11 years (OR = 1.17, 95% CI (1.06, 1.32)) and a significant cumulative RSEI score effect (OR = 1.30, 95% CI (1.02, 1.84)) for long-term residents in Detroit, where benzene and trichloroethylene were the most important chemicals driving this association.” Large weights for dichloromethane (methylene chloride) in models of cumulative exposure also supported evidence for its association with NHL risk. The authors conclude that this study adds to the carcinogenicity evidence for benzene, trichloroethylene, and

dichloromethane [methylene chloride] and NHL.

Petitioner's Assessment: This study reinforces the carcinogenicity evidence for benzene, methylene chloride, and trichloroethylene.

- b. *Malavolti M, Malagoli C, Filippini T et al. Residential Proximity to Petrol Stations and Risk of Childhood Leukemia. Eur J Epidemiol 2023;38:771-782.*

This population-based case-control study in Northern Italy included 182 cases of childhood leukemia diagnosed between 1998 and 2019 and 726 age- and sex-matched population controls. Leukemia risk was estimated according to distance from petrol stations with a 1000 m buffer and amount of supplied fuel within a buffer of 250 m from the child's residence. The researchers concluded that the relative risk of childhood leukemia was 2.2 (95% CI 0.5–9.4) for children living <50 m from the nearest petrol station, compared with children who lived ≥ 1000 meters from a petrol station. "Associations were stronger for the ALL [acute lymphoblastic leukemia] subtype (RR=2.9, 95% CI 0.6–13.4) and among older children (age ≥ 5 years: RR=4.4, 95% CI 0.6–34.1; age<5 years: RR=1.6, 95% CI 0.1–19.4). Risk of leukemia was also greater (RR=1.6, 95% CI 0.7–3.3) among the most exposed participants when assigning exposure categories based on petrol stations located within 250 m of the child's residence and total amount of gasoline delivered by the stations. Overall, residence within close proximity to a petrol station, especially one with more intense refueling activity, was associated with an increased risk of childhood leukemia, although associations were imprecise." (In other words, confidence intervals were large and spanned less than and greater than 1.0).

Petitioner's Assessment: This study, while not conclusive, is consistent with the evidence linking benzene and childhood leukemia.

- c. *Nethery RC, Vega S, Frazier AL, Laden F. Mobile Source Benzene Regulations and Risk of Childhood and Young Adult Hematologic Cancers in Alaska: A Quasi-Experimental Study. Epi 2023;34:385-388.*

EPA's Mobile Source Air Toxics rules (MSAT) were implemented in 2011 and produced a dramatic decline in ambient benzene in Alaska. The authors sought to evaluate its impact on childhood and young adult leukemia and lymphoma incidence in Alaska. "Due to previously enacted benzene regulations in the continental United States, MSAT had relatively modest impacts in other states," according to the authors. "Using 2-year state-level incidence rates of childhood and young adult leukemia and lymphoma," the authors "found evidence of a substantial reduction associated with MSAT in incidence of childhood and young adult lymphoma (-1.23 [-1.84, -0.62] cases per 100,000)." There was a slight but indeterminate reduction in leukemia (-0.13 [-0.77, 0.51] cases per 100,000). The authors note that the primary limitation of the study is "the small population of Alaska, which when coupled with these relatively rare diseases, results in small case counts and noisy temporal trends." They conclude that confirmatory studies in larger populations are needed, and that subtype specific analyses may provide additional insights, but that their findings are consistent with the hypothesis that MSAT, which reduced benzene levels in Alaska, led to a decline in lymphoma incidence in children and young adults.

Petitioner's Assessment: This study is consistent with the hypothesis that reductions in benzene led to a decline in lymphoma incidence in children and young adults and supports the link between benzene and hematologic cancers.

- d. *Goldberg MS, Zapata-Marin S, Labrèche F et al. Ambient Exposures to Selected Volatile Organic Compounds and the Risk of Prostate Cancer in Montreal. Environ Epi 2022;6:e231.*

This study is based on a population-based case-control study of incident prostate cancer (PROtEuS) in men ≤ 75 years of age living in Montreal, Canada, in 2005 to 2012. It included 1172 cases and 1177 population controls. The authors had personal information, lifetime residential addresses, occupational exposures, and a variety of area-wide covariables. They inferred concentrations of five ambient volatile organic compounds (VOCs) including benzene using Bayesian geostatistical models and data from a dense environmental survey conducted in Montreal in 2005 to 2006. They used different sets of adjustments to estimate odds ratios (OR) and confidence intervals. They found nonlinear associations such that the ORs increased monotonically and then either flattened or fell off with increased exposures. The model that contained other environmental variables and contextual variables led to lower ORs and results were similar when they restricted analyses to controls recently screened or tested for prostate cancer or cases with low- or high-grade tumors. A change from the 5th to 25th percentile in mean environmental benzene levels led to an adjusted OR of 2.00 (95% confidence interval = 1.47, 2.71). The authors conclude that they found positive associations between prostate cancer and concentrations of benzene, independently of previous testing for prostate cancer or tumor grade, suggesting that exposure to benzene may increase incidence.

Petitioner's Assessment: This relatively large study provides some (limited) evidence to expand the types of cancer that benzene may cause to include prostate cancer.

2. Animal studies

(no additional studies identified)

3. Genotoxicity and mechanistic studies

- a. *Dai K, Wang C, Yao W, Hao C. Expression Level and Function Analysis of Serum miRNAs in Workers with Occupational Exposure to Benzene Series. Chemosphere 2023;313:137460.*

MicroRNAs (miRNAs) have been useful as biomarkers of a variety of diseases and exposure to carcinogens. The purpose of this study was to explore the distribution characteristics and biological function of miRNAs in subjects exposed to benzene series (BTEX; benzene, toluene, ethylbenzene, xylene, styrene). “In this study, serum miRNAs were measured in 247 occupationally exposed subjects and 256 controls. The relationship between cumulative exposure dose of benzene series and miRNAs was analyzed by Generalized linear model, Spearman’s rank correlation, and chi-square test for trend. The function of MiRNAs target gene was analyzed by means of bioinformatics method. The results showed that the expressions of miR-181a-5p, 221-3p, 223-3p, and 342-3p were down-regulated, whilst the expression of miR-638 was upregulated in the occupational exposure group.” All of these five miRNAs (miR-181a-5p, 221-3p, 223-3p, 342-3p, and 638) showed dose-response relationship with benzene series, and were closely related to multiple tumor pathways, including leukemia. Previous studies in animals and humans have found that benzene affected many of these same miRNAs. These five miRNAs “may be involved in the carcinogenic process of benzene series and could be used to evaluate the

early biological effects and monitor the exposure level of benzene series. miRNAs are potential biomarkers of benzene series exposure.”

Petitioner’s Assessment: This study is not exclusively focused on benzene but suggests that miRNA may play a role in the carcinogenesis of benzene and other members of the benzene series.

- b. *Lin D, Wang D, Li P et al. Whole-Exome Sequencing Identified Recurrent and Novel Variants in Benzene-Induced Leukemia. BMC Med Genomics 2023;16:13.*

This study included 10 patients with benzene-induced leukemia (BIL). The authors conducted whole-exome sequencing on their peripheral blood samples. (An exome is the sequence of all the exons in a genome, reflecting the protein-coding portion of a genome, according to NIH¹⁸⁵.) The sequencing data they obtained were screened for potential pathogenic and novel variants, and then the variants-located genes were clustered to identify cancer-related pathways. Any variants among the BIL cases that were shared or recurrent were also identified and evaluated for their potential functional impact. The authors “identified 48,802 variants in exons in total, 97.3% of which were single nucleotide variants. They obtained 8,667 potentially pathogenic variants (after filtering out variants with minor allele frequency $\geq 1\%$), of which 174 were shared by all the BIL cases. “The identified variants were located in genes that could be significantly enriched into certain cancer-related pathways such as PI3K-AKT signaling pathway and Ras signaling pathway.” The authors also identified 1010 novel variants with no record in the Genome Aggregation Database and in the Database of Short Genetic Variation. One was shared by 90% of cases, and “caused a missense mutation in SESN3.” The authors concluded that they “examined variations of the whole exome in BIL patients for the first time;” and that the commonly shared variants implied a relation with BIL; and that the recurrent and novel variant might be specifically related to BIL.

Petitioner’s Assessment: This study provides genetic clues that should prove useful for better understanding mechanisms underlying benzene induced leukemia.

- c. *Lu Y, Sui P, Li J et al. Benzene Metabolite Hydroquinone Enhances Self-Renewal and Proliferation of Preleukemic Cells Through the Ppar γ Pathway. Toxicol Letters 2023;382:33-40.*

In this study, preleukemic bone marrow (PBM) cells derived from transgenic mice carrying a gene associated with acute myeloid leukemia (Mll–Af9 fusion gene) were treated with the benzene metabolite hydroquinone (HQ) in a serial replating of colony forming unit (CFU) assay. RNA sequencing was used to identify the potential key genes contributing to benzene-initiated self-renewal and proliferation. The researchers found that HQ “induced a significant increase in colony formation in PBM cells,” and that “the peroxisome proliferator-activated receptor gamma (Ppar- γ) pathway, which plays a critical role in carcinogenesis in multiple tumors, was significantly activated” after HQ treatment. They conclude that the results, “provide insight into the missing link between premalignant status and development of benzene-induced leukemia.”

¹⁸⁵ NIH National Human Genome Research Institute. Exome. Undated. <https://www.genome.gov/genetics-glossary/Exome>.

Petitioner's Assessment: This study sheds light on how Ppar γ activation by the benzene metabolite hydroquinone plays a role in the development of cancer.

- d. Sayed AE-D, Idriss SK, Abdel-Ghaffar SKh, Hussein AAA. *Haemato-Biochemical, Mutagenic, and Histopathological Changes in Oreochromis niloticus Exposed to BTX. Environ Sci Pollution Res 2023;30:59301-59315.*

Nile Tilapia (*Oreochromis niloticus*) were randomly distributed after an adaptation period into four groups and kept in glass containers having the same volume of water. Group 1 were fed the control diet, Group 2 were exposed to benzene (0.762 ng/L) for 15 days, and the other groups were exposed to toluene or xylene for 15 days. A random sample of six fish from each group were selected after 15 days, ice anesthesia was administered, and blood collected from the caudal vein. Exposure to benzene and induced DNA damage, as measured by the Comet assay, as did toluene and xylene. Histopathological changes, changes in haemato-biochemical parameters, and antioxidant alterations were observed as well.

Petitioner's Assessment: Benzene damaged DNA in fish under the conditions of this study, which provides additional support for the genotoxicity of benzene, a key characteristic of carcinogens.¹⁸⁶

- e. Xuan M, Wu Y, Wang H et al. *Effect of mir-92a-3p on Hydroquinone Induced Changes in Human Lymphoblastoid Cell Cycle and Apoptosis. Environ Toxicol 2023;381420-1430.*

Hydroquinone (HQ) is one of the metabolites of benzene in humans, and chronic exposure to it can lead to leukemia. In a previous study by this group, the authors “constructed a model of malignant transformation of human lymphoblastoid cells (TK6) induced by chronic exposure to HQ with significant subcutaneous tumorigenic capacity in nude mice.” In the present study, miR-92a-3p, a tumor factor, was found to “target and regulate [the anti-proliferative factor] TOB1, and the expression level of miR-92a-3p was significantly upregulated in the long-term HQ-induced TK6 malignant transformation model, while TOB1 ... was significantly downregulated.” To investigate the mechanism behind this, the researchers “inhibited miR-92a-3p in the malignant transformation model and found a decrease in cell viability, a decrease in MMP-9 protein levels, a G2/M phase block in the cell cycle, and an upregulation of the expression of G2/M phase-related proteins cyclinB1 and CDK1. Inhibition of miR-92a-3p in combination with si-TOB1 restored cell viability, inhibited cyclin B1 and CDK1 protein levels, and attenuated the G2/M phase block. Taken together, miR-92a-3p reduced the cell proliferation rate of the malignantly transformed cells (HQ19) and caused cell cycle arrest by targeting TOB1, which in turn contributed to the altered malignant phenotype of the cells.” The authors concluded that this study “suggests that miR-92a-3p is likely to be a biomarker for long-term HQ-induced malignant transformation of TK6 and could be a potential therapeutic target for leukemia. caused by long-term exposure to HQ.”

Petitioner's Assessment: This study points to the possible role of a type of microRNA (miR-92a-3p) in leukemia induced by hydroquinone, a metabolite of benzene.

¹⁸⁶ IARC, Preamble to the IARC Monographs (amended January 2019), p. 27, at <https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/>.

- f. Yang X, Dong S, Li C et al. Hydroquinone Triggers Pyroptosis and Endoplasmic Reticulum Stress Via AhR-Regulated Oxidative Stress in Human Lymphocytes. *Toxicol Letters* 2023;376:39-50.

Hydroquinone (HQ) is one of the main reactive metabolites of benzene, and can activate the aryl hydrocarbon receptor (AhR), which is essential for HQ-induced toxicity, including apoptosis and DNA damage. Since AhR is an important regulator of the immune system, this study examined how HQ-induced AhR activity affected inflammation. It found that HQ could cause inflammation and induced endoplasmic reticulum stress (ERS) by releasing excessive reactive oxygen species (ROS). Chronic inflammation is thought to be one of the symptoms of cancer, accelerating the progression of normal to malignant cells. The authors conclude that AhR-mediated HQ-induced ERS, ROS and inflammasome activation may play vital roles in the effects of benzene.

Petitioner's Assessment: This study work provides insights into potential molecular mechanisms underlying benzene carcinogenicity.

- g. Phillips RV, Wei L, Cardenas A et al. Epigenome-Wide Association Studies of Occupational Exposure to Benzene and Formaldehyde. *Epigenetics* 2022;17(3):2259-2277.

This analysis included a cross-sectional epigenome-wide study of 50 workers exposed to benzene and 48 controls and examined differences in blood cell DNA methylation. Genome-wide statistically significant alterations were found between exposed workers and controls, and pathway analysis of genes corresponding to benzene-associated differential methylation sites revealed an impact on signaling pathways, including primarily the AMP-activated protein kinase, or AMPK signaling pathway. The authors state that increased DNA methylation variability has been associated with cancer progression, citing Teschendorff et al. 2016.¹⁸⁷ The authors conclude that their findings support the links between benzene exposure and cancer.

Petitioner's Assessment: This study adds to the evidence that benzene exposure results in specific DNA methylation patterns that may play a role in benzene-induced cancers.

4. Reviews

- a. Francisco LFV, da Silva RN, Olivereira MA et al. Occupational Exposures and Risks of Non-Hodgkin Lymphoma: A Meta-Analysis. *Cancers (Basel)* 2023; 15(9):2600.

This meta-analysis included 51 articles examining the association between occupational exposure to carcinogens and risk of non-Hodgkin lymphoma (NHL), resulting in an overall OR of 1.27 (95% CI 1.04-1.55). The authors found that the risk of NHL increases for individuals occupationally exposed to chemical agents, benzene, and trichloroethylene, as well as for certain work classes. It concluded that there is still insufficient data on the association between NHL and specific chemical compounds.

Petitioner's Assessment: This meta-analysis did not examine the risk from benzene specifically but found that the risk of NHL increases for individuals occupationally exposed to chemical agents, including benzene, and is thus consistent with the evidence

¹⁸⁷ Teschendorff AE, Gao Y, Jones A, et al. DNA Methylation Outliers in Normal Breast Tissue Identify Field Defects that are Enriched in Cancer. *Nat Commun.* 2016;7:10478.

that benzene causes cancer, specifically NHL.

- b. Galatro D, Trigo-Ferre R, Nakashook-Zettler A et al. *Framework for Evaluating Potential Causes of Health Risk Factors Using Average Treatment Effect and Uplift Modelling. Algorithms 2023;16:166.*

Benzene exposure has been reported to increase the risk of developing acute myeloid leukemia (AML) in children and occupationally exposed adults. Such assessments have been documented in the literature using odds ratios and/or risk ratios, with data fitted to unconditional logistic regression. “Although statistical causal analysis is commonly used to determine causation by evaluating a distribution’s parameters, it is challenging to infer causation in complex systems from single correlation coefficients. Machine learning (ML) approaches, based on causal pattern recognition,” the authors argue, “can provide an accurate alternative to model counterfactual scenarios.” In this work, the authors “propose a framework using average treatment effect (ATE) and Uplift modeling to evidence causation when relating exposure to benzene indoors and outdoors to childhood AML, effectively predicting causation when exposed indoors to this contaminant. An analysis of the assumptions, cross-validation, sample size, and interaction between predictors are also provided,” in the hopes of future work using this approach to predict health outcomes.

Petitioner’s Assessment: This analysis reinforces the evidence that benzene causes cancer, specifically, AML in children.

- c. Micallef CM, Charvat H, Houot M-T et al. *Estimated Number of Cancers Attributable to Occupational Exposures in France in 2017: An Update Using a New Method for Improved Estimates. J Exposure Sci Environ Epi 2023;33:125-131.*

In this analysis, population-level prevalence of lifetime exposure to ten carcinogens, including benzene and trichloroethylene, and two occupational circumstances were estimated using the French Census linked with job-exposure matrices and French occupational surveys. Lifetime prevalence of exposure was defined as the proportion of the population alive in 2017 ever exposed to an agent over the defined exposure period. The population attributable fraction estimates the contribution of a risk factor in the occurrence of a disease at the population level and reflects both the prevalence of the exposure and the magnitude of the association between the risk factor and the outcome. For benzene and acute myeloid leukemia (AML) in men, the authors reported an estimated lifetime prevalence over 1997-2017 of 2.1, a population attributable fraction of 2.6 (95% CI: 0.8-5.4), the number of incident cases as 1600, and the number of attributable cases as 41 (95% CI: 12-86). For women, the estimates were far smaller.

Petitioner’s Assessment: This analysis is consistent with the evidence that occupational exposures to benzene causes cancer, specifically AML.

- d. Vallée M. *How Government Health Agencies Obscure the Impact of Environmental Pollution and Perpetuate Reductionist Framings of Disease: The Case of Leukemia. Int J Soc Determinants Health Serv 2023; 27551938231169119.*

This analysis analyzes how three health agencies (Cancer Australia, the U.S. National Institutes of Health, and the United Kingdom’s National Health Service) framed leukemia in information provided to the public, including their coverage of toxicants linked to leukemia. The author focuses on leukemia since it is strongly linked to benzene and other toxicants,

impacts numerous people, and may be unequally distributed. The paper includes a brief summary of the evidence linking benzene and leukemia, citing IARC, studies demonstrating a dose-response relationship between it and the cancer, and other studies supporting the link to cancer. They conclude that the information offered by these health agencies fails to identify most toxicants linked to leukemia by emphasizing a biomedical framing of the condition, and discusses the social consequences and sources of the problem. The NIH website failed to mention benzene and other toxicants other than radiation therapy and exposure to high levels of radiation, despite the strong evidence linking benzene and leukemia. Benzene was included in coverage by the other two agencies examined. However, those sites failed to identify sources of benzene.

Petitioner's Assessment: This analysis, while not a comprehensive scientific assessment of evidence linking benzene and leukemia, highlights some of the key evidence and conclusions supporting the link, and in particular highlights the need for better communication to the public so that appropriate measures to eliminate or limit exposure might be taken.

- e. Yusoff NA, Hamid ZA, Budin SB, Taib IS. Linking Benzene, in Utero Carcinogenicity and Fetal Hematopoietic Stem Cell Niches: A Mechanistic Review. *Int J Mol Sci* 2023;24:6355.

The mechanism of in utero carcinogenicity by benzene in targeting fetal hematopoietic stem and progenitor cells (HSPCs) is the primary focus of this review, which is based on 199 references. HSPCs are parental blood cells that regulate hematopoiesis during the fetal and adult stages. The authors conclude that accumulating evidence suggests that benzene and its reactive metabolites are risk factors for in utero carcinogenicity, and that benzene and/or its metabolites act via multiple modes of action targeting the adult HSPC niche. “However, there is a lack of evidence linking the mechanism of benzene toxicity with in utero carcinogenicity targeting the HSPC niches.” Oxidative stress, chromosomal aberration and epigenetic modification are among the known mechanisms mediating benzene-induced genetic and epigenetic modification in fetal stem cells leading to in utero carcinogenesis. The authors call for research focused on in utero carcinogenicity by benzene to better understand the potential molecular signature of cancer stem cells, as the developing fetus is highly susceptible.

Petitioner's Assessment: This review provides mechanistic support for the in utero carcinogenicity of benzene.

Although not about the ability of benzene to cause or promote cancer, we note that there are many studies indicating widespread non-occupational as well as occupational exposures to benzene, including one that raises concerns about the potential risk associated with benzene for people who spend a significant time in their vehicles.¹⁸⁸ This further underscores the need to eliminate all unnecessary exposures to reduce overall risk.

B. Ethylene Dichloride

No additional studies on the ability of ethylene dichloride to cause or promote cancer were identified.

¹⁸⁸ Reddam A, Volz DC. Inhalation of two Prop 65-listed chemicals within vehicles may be associated with increased cancer risk. *Env Int* 2021; 149:106402.

C. Methylene Chloride

Only one additional study on the ability of methylene chloride to cause or promote cancer was identified, which has also been described under benzene and trichloroethylene, which reinforces the evidence that methylene chloride causes cancer:

- a. Boyle J, Ward MH, Cerhan JR et al. *Modeling Historic Environmental Pollutant Exposures and Non-Hodgkin Lymphoma Risk. Environ Res* 2023;224:115506.

This study (also described above under benzene) examined associations between non-Hodgkin lymphoma (NHL) and historic environmental pollutant emissions from the Risk Screening Environmental Indicators (RSEI) model, which uses an EPA database of toxic release emissions to air, water, and land. (It also looked at the association between NHL and chemical mixtures measured in house dust, but these did not include methylene chloride). Participants were enrolled in the NCI Surveillance, Epidemiology, and End Results (SEER) population-based case-control study (1998-2000) at four SEER centers: Detroit, Iowa, Los Angeles County, and Seattle, and included 1,321 cases of NHL aged 20-74 years who were diagnosed between July 1, 1998 and June 30, 2000 and 1,057 population-based controls matched to cases by age within 5-year groups, sex, race, and study center. Researchers found a “significant positive association between RSEI scores and NHL at the maximum time lag of 11 years (OR = 1.17, 95% CI (1.06, 1.32)) and a significant cumulative RSEI score effect (OR = 1.30, 95% CI (1.02, 1.84)) for long-term residents in Detroit, where benzene and trichloroethylene were the most important chemicals driving this association.” Large weights for dichloromethane (methylene chloride) in models of cumulative exposure also supported evidence for its association with NHL risk. The authors conclude that this study adds to the carcinogenicity evidence for benzene, trichloroethylene, and dichloromethane [methylene chloride] and NHL, for which IARC noted positive associations but did not consider them to be “sufficient” evidence for NHL.

Petitioner’s Assessment: This study reinforces the carcinogenicity evidence for methylene chloride and NHL.

We also note a 2023 study¹⁸⁹ that found that methylene chloride was one of two out of 18 priority volatile organic chemicals most prevalent in consumer products. Methylene chloride was found in paint removers, lubricants, adhesives, cleaners, hand dishwashing soap, and personal care products. As the study notes, it is now banned in consumer paint strippers. It is still used in the workplace.

D. Trichloroethylene (TCE):

We found ten human studies, two animal studies, three genotoxicity or mechanistic studies, and six reviews on the ability of trichloroethylene to cause or promote cancer. We briefly describe each study or review below.

As might be expected for a chemical that has been designated a known carcinogen, no studies in the recent literature dispute or contradict the assertion that trichloroethylene is carcinogenic. One review that focused specifically on multiple myeloma did not find evidence of an association with trichloroethylene,

¹⁸⁹ Knox KE, Dodson RE, Rudel RA et al. Identifying Toxic Consumer Products: A Novel Data Set Reveals Air Emissions of Potent Carcinogens, Reproductive Toxicants, and Developmental Toxicants. *Environ Sci Technol* 2023, 57:7454-7465.

but all the others reinforce, support, are consistent with, or extend the evidence on the carcinogenicity of trichloroethylene.

1. Human studies

- a. Boyle J, Ward MH, Cerhan JR et al. *Modeling Historic Environmental Pollutant Exposures and Non-Hodgkin Lymphoma Risk. Environ Res* 2023;224:115506.

This study (described above) examined associations between non-Hodgkin lymphoma (NHL) and historic environmental pollutant emissions from the Risk Screening Environmental Indicators (RSEI) model, which uses an EPA database of toxic release emissions to air, water, and land. (It also looked at the association between NHL and chemical mixtures measured in house dust, but these did not include TCE.). Participants were enrolled in the NCI Surveillance, Epidemiology, and End Results (SEER) population-based case-control study (1998-2000) at four SEER centers: Detroit, Iowa, Los Angeles County, and Seattle, and included 1,321 cases of NHL aged 20-74 years who were diagnosed between July 1, 1998 and June 30, 2000 and 1,057 population-based controls matched to cases by age within 5-year groups, sex, race, and study center. Researchers found a “significant positive association between RSEI scores and NHL at the maximum time lag of 11 years (OR = 1.17, 95% CI (1.06, 1.32)) and a significant cumulative RSEI score effect (OR = 1.30, 95% CI (1.02, 1.84)) for long-term residents in Detroit, where benzene and trichloroethylene were the most important chemicals driving this association. Large weights for dichloromethane (methylene chloride) in models of cumulative exposure also supported evidence for its association with NHL risk. The authors conclude that this study adds to the carcinogenicity evidence for benzene, trichloroethylene, and dichloromethane [methylene chloride] and NHL, for which IARC noted positive associations but did not consider them to be “sufficient” evidence for NHL.

Petitioner’s Assessment: This study reinforces the evidence that trichloroethylene causes cancer, specifically NHL.

- b. Andrew AS, Li M, Shi X et al. *Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. J Environ Res Public Health* 2022;19:618.

The study included 292 kidney cancer cases and 448 age-, gender-matched controls in New Hampshire, identified from the Dartmouth-Hitchcock Health System. Using publicly available data on TCE levels in groundwater, the researchers modeled the spatial dispersion and temporal decay and overlaid locations of cases and controls with yearly maps of estimated TCE levels to estimate exposures over 5, 10, and 15-year periods before diagnosis. The 50th-75th percentile of estimated residential exposure over a 15-year period was associated with increased kidney cancer risk (OR=1.78, 95% CI: 1.05-3.03) compared to <50th percentile.

Petitioner’s Assessment: This study adds to the evidence that trichloroethylene causes cancer, specifically kidney cancer.

- c. Chuang Y-S, Lee C-Y, Lin P-C et al. *Breast Cancer Incidence in a National Cohort of Female Workers Exposed to Special Health Hazards in Taiwan: A Retrospective Case-Cohort Study of ~300,000 Occupational Records Spanning 20 Years. Int Arch Occup Environ Health* 2022;95:1979-1993.

This was a retrospective study of 4,774,295 workers in Taiwan identified from Taiwan's Ministry of Labor's Especially Exposed Workers (EEW) database between 1997 and 2018 and Taiwan's Cancer Registry between 1997 and 2016. The study focused on the risk of breast cancer, now the most common cancer among women worldwide. A total of 3,248 female workers with breast cancer and 331,967 without breast cancer were included. Standardized Incidence Ratios (SIRs), which estimate "the number of cancer cases in a given population compared to what might be "expected" based on a comparison with the cancer experience in a larger population,"¹⁹⁰ were calculated for women exposed to different hazards, and breast cancer incidence rate ratios (IRRs) were calculated, adjusting for age and duration of exposure. For trichloroethylene/tetrachloroethylene, the SIR was 1.47 (95% CI 1.12–1.82) and the adjusted IRR was 1.42 (95% CI 1.12–1.81), indicating an association between trichloroethylene/tetrachloroethylene and breast cancer.

Petitioner's Assessment: This study is consistent with the evidence that trichloroethylene causes cancer, although some portion of the cancers may have been caused by tetrachloroethylene.

- d. Weinstein B, Da Silva A, Carpenter DO. Exocrine Pancreatic Cancer and Living Near to Waste Sites Containing Hazardous Organic Chemicals, New York State, USA – An 18-Year Population Study. *Int J Occup Med Environ Health* 2022;35(4):459-471.

The authors of this ecologic study identified 28,941 patients diagnosed with exocrine pancreatic cancer in New York State exclusive of New York City for the years 1996-2013 and compared hospitalization rates among patients who lived in zip codes with hazardous waste sites (HWSs) containing persistent organic pollutants and volatile organic pollutants with "clean" zip codes with no identified HWSs. In the analysis by specific chemicals, after adjustment for potential confounders, the rate ratio (RR) for benzene was 1.12 and trichloroethylene was 1.07, indicating an elevated risk of being hospitalized for exocrine pancreatic cancer. The exposures in this study are much lower than seen in occupational settings.

Petitioner's Assessment: This study is consistent with the evidence that trichloroethylene causes cancer.

- e. Tessema ST, Mahgoub AE, Nakhleh R. Angiosarcoma: A Rare Malignancy Linked to Chemical Exposures. *Cureus* 2022;14(5):e25289.

This case study documents angiosarcoma, an exceptionally rare malignancy that accounts for less than 1% of all sarcomas, in a 90-year-old male veteran who was likely exposed to TCE and other chemicals, including tetrachloroethylene, trans-1,2-dichloroethylene, and vinyl chloride.

Petitioner's Assessment: This case study is consistent with the evidence that trichloroethylene causes cancer, although other chemicals may have been responsible in whole or in part for the cancer observed in this individual.

¹⁹⁰ CDC. Standardized Incidence Ratio (SIR): A Math-based Approach to Evaluating Unusual Patterns of Cancer. November 16, 2022. <https://www.cdc.gov/nceh/cancer-environment/pdfs/standardized-incidence-ratio-fact-sheet-508.pdf>.

- f. *Li N, Zhai Z, Zheng Y et al. Association of 13 Occupational Carcinogens in Patients with Cancer, Individually and Collectively, 1990-2017. JAMA Netw Open 2021;4(2):e2037530.*

This cross-sectional study included data from 195 countries obtained from the Global Burden of Diseases, Injuries, and Risk Factors (GBD) Study from the beginning of 1990 to the end of 2017. Based on the GBD study, TCE was one of 13 occupational carcinogens attributable to 7 cancer types. Exposure to TCE was attributable to kidney cancer, based on evidence rules, meaning that the association has been verified by published meta-analyses or pooled studies; or if those did not exist, key single studies. The global age-standardized summary exposure for TCE in patients with cancer increased 30.3% (95% UI:27.3%-33.5%) from 1990 to 2017 – one of only two occupational carcinogens that increased by more than 30% during that time period.

Petitioner's Assessment: This study reinforces the evidence that trichloroethylene causes cancer, specifically kidney cancer.

- g. *Purdue MP, Rhee J, Moore L et al. Differences in Risk Factors for Molecular Subtypes of Clear Cell Renal Cell Carcinoma. Int J Cancer 2021;149:1448-1454.*

This case-control study in Eastern Europe and meta-analysis analyzed risk factors for ccA and ccB molecular subtypes of clear cell renal cell carcinoma (ccRCC). Risk factors considered included age, sex, BMI, smoking, hypertension, occupational exposure to trichloroethylene, family history of kidney cancer, and single-nucleotide polymorphisms (SNPs) associated with renal cancer. The case-control study included 144 ccA cases and 106 ccB cases and 1476 controls. The meta-analysis summarized case-only results from this study and three patient cohorts. Trichloroethylene was associated with ccB but not ccA (OR 3.09, 95% CI: 1.11-8.65 and 1.25, 0.36-4.39 respectively for ≥ 1.58 ppm-years vs unexposed). Patients with ccB tumors had poorer survival than those with ccA tumors and were more likely to be male (case-only odds ratio [OR] 2.68, 95% confidence interval [CI] 1.43-5.03). In case-control analyses, body mass index was significantly associated with ccA tumors (OR 2.45, 95% CI 1.18-5.10 for ≥ 35 vs < 25 kg/m²) but not with ccB tumors (1.52, 0.56-4.12). In the meta-analysis, the ccB cases were still more likely to be male and ccA cases more likely to be obese.

Petitioner's Assessment: This study reinforces the evidence that trichloroethylene causes cancer, specifically a subtype of clear cell renal cell cancer.

- h. *Pedersen JE, Strandberg-Larsen K, Andersson M, Hansen J. Occupational Exposure to Specific Organic Solvents and Risk of Subtypes of Breast Cancer in a Large Population of Danish Women, 1964-2016. Occup Environ Med 2020;78:192-198.*

The study included 38,375 women under age 70 years with primary breast cancer, identified from the Danish Cancer Registry, and five randomly selected breast cancer-free controls per case matched on year of birth identified from the Danish Civil Registration System. A nationwide pension fund was used to identify exposure to TCE, benzene, toluene, and 1,1,1-trichloroethane. After age 50 years, exposure to TCE was associated with a small increased risk of breast cancer in women with over 20 years of latency (OR = 1.26, 95% CI: 1.02-1.56). Further, an increased risk of estrogen receptor positive tumors was also observed (OR = 1.21, 95% CI: 1.01-1.47), and high cumulative exposure and longer latency also increased the risk of this subtype.

Petitioner's Assessment: This study reinforces the evidence that trichloroethylene causes cancer, specifically breast cancer.

- i. *Lyng E, Kaerlev L, Olsen J et al. Rare Cancers of Unknown Etiology: Lessons Learned from a European Multi-Center Case-Control Study. Eur J Epidemiol 2020;35:937-948.*

This European, multi-center case-control study of occupational risks for rare cancers, including cancers of small intestine, bone sarcoma, uveal melanoma, mycosis fungoides, thymus, male biliary tract, and breast, reported an association between TCE (high exposure) and male breast cancer, OR 1.9 (95% CI 1.1-3.3). Participants included 29 cases of 336 exposed and 75 cases of 1669 unexposed. No association was observed between low exposure to TCE and male breast cancer. The researchers concluded that the association deserved further scrutiny.

Petitioner's Assessment: This study is consistent with the evidence that trichloroethylene causes cancer, specifically male breast cancer.

2. Animal Studies

- a. *Abdraboh ME, El-Missiry MA, Othman AI et al. Constant Light Exposure and/or Pinealectomy Increases Susceptibility to Trichloroethylene-Induced Hepatotoxicity and Liver Cancer in Male Mice. Environ Sci Pollut Res 2022;29:60371-60384.*

Ten groups of adult male albino mice, 5 mice/group, were studied for 30 days. Two groups were control animals: no TCE treatment and exposed to 12 hours light/12 hours dark each day; and no TCE treatment and exposed to constant light. One was a sham control: no TCE treatment, exposed to 12 hours light/12 hours dark, and subjected to surgery without removal of the pineal gland. One was identical to the first control group except the pineal gland was removed surgically. Three groups were exposed to 500 mg TCE daily by stomach tube for 6 days, then left without treatment for the remainder of the experiment, and exposed to either 12 hour light/12 hour dark cycle, constant light, or pinealectomized and exposed to 12 hour light/12 hour dark cycle. The remaining three groups were the same as the last three except they were given 1,000 mg TCE instead of 500 mg. Melatonin levels were significantly decreased in both pinealectomized and TCE-treated animals at both light regimens. Aspartate transaminase, alanine aminotransferase, and serum bilirubin levels were significantly elevated, and albumin levels markedly decreased, in pinealectomized and TCE-treated animals, and the combination group. Histopathological analysis indicated liver injury and induction of liver cancer. "These effects were accompanied by a significant increase of the liver cancer biomarker alpha-fetoprotein and the expression of the metastatic markers CD44 [a cell surface protein that is overexpressed in cancer cells¹⁹¹], TGFβ-1 (transforming growth factor beta-1), and VEGF (vascular endothelial growth factor), along with increased oxidative stress indicators and inflammatory cytokines (IL-6, IL-1β, and TNF-α) in both pinealectomized and TCE-treated animals and the combination group at both light regimens." The authors conclude that, "low melatonin levels, exposure to constant light, and the combination of both factors increase susceptibility to the toxic and carcinogenic effects of TCE on the liver."

¹⁹¹ Thapa R, Wilson GD. The Importance of CD44 as a Stem Cell Biomarker and Therapeutic Target in Cancer. *Stem Cells Int* 2016;2016:2087204.

Petitioner's Assessment: This study is consistent with the evidence that trichloroethylene causes cancer.

- b. *Li SP, Chang QQ, Ren XH et al. Induction of Hepatocellular Carcinoma in B6C3(F1) Mice Chronically Exposed to Trichloroethylene with Enhanced Acetylation of Histone H2AK9ac and SET Expression in the Liver Tissue. Chinese J Industrial Hygiene Occup Dis [Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi] 2021;39(12):910-914. [article in Chinese]*

B6C3 mice at 6 weeks were treated with TCE at 500, 1000, and 2000 mg/kg doses by gastric gavage, with corn oil used as the negative control and carbon tetrachloride as the positive control for 56 weeks. Statistical increases in the incidence of hepatocellular carcinoma compared to control were observed ($p < 0.01$) in a dose-dependent manner. The study aimed to establish an animal model of TCE-induced liver cancer and “to understand changes in expression of SET [an oncoprotein¹⁹²] and histone acetylation, potentially serving as a molecular mechanism for TCE-induced hepatocarcinogenesis.” At the two highest doses, levels of SET and histone H2AK9ac were increased ($p < 0.05$), while HDAC1 (an enzyme that catalyzes the deacetylation of histones¹⁹³) was decreased ($p < 0.05$). We were only able to review the abstract as the article is in Chinese.

Petitioner's Assessment: This study reinforces the evidence that trichloroethylene causes cancer.

3. Genotoxicity and Mechanistic Studies

- a. *Hosgood HD, Rahman ML, Blansky D et al. Targeted proteomic scan identifies alteration of serum proteins among workers occupationally exposed to low levels of trichloroethylene. Environ Mol Mutagen 2022;63(8-9):423-428.*

This cross-sectional molecular epidemiology study included data of 1317 targeted proteins in serum from 42 TCE exposed and 34 unexposed factory workers in Guangdong, China to better understand molecular mechanisms of non-Hodgkin's lymphoma (NHL) induced by TCE. Occupational exposure to TCE was associated with lower levels of tumor necrosis factor receptor superfamily member 17 ($p = 0.003$), a key B-cell maturation antigen that mediates B-cell survival, and kynureninase ($p = 0.002$), an enzyme that plays a role in T-cell mediated immune response. These proteins also showed a significant exposure-response relation across unexposed, low exposed, and high exposed worker (all p -trends < 0.001).

Petitioner's Assessment: This study provides insights into possible mechanisms through which trichloroethylene causes cancer, specifically NHL.

- b. *Zhang J, Wang W, Pei Z et al. Mutagenicity Assessment to Pesticide Adjuvants of Toluene, Chloroform, and Trichloroethylene by Ames Test. Int J Environ Res Public Health 2021;18:8095.*

¹⁹² Bayarkhangai B, Noureldin S, Yu L et al. A Comprehensive and Perspective View of Oncoprotein SET in Cancer. *Cancer Med* 2018;7(7):3084-3094.

¹⁹³ NIH National Center for Biotechnology Information. HDAC1 histone deacetylase 1. <https://www.ncbi.nlm.nih.gov/gene/3065>.

TCE was mutagenic in the Ames test (*Salmonella typhimurium* reverse mutation test) with and without rat liver microsomal preparations (S9) in the TA97, TA98, and TA100 strain. In the TA102 strain, TCE was only mutagenic at the highest dose tested without S9. TCE caused mutagenicity at a lower dose than toluene or chloroform.

Petitioner's Assessment: This study, which found that trichloroethylene is mutagenic, is consistent with the evidence that trichloroethylene causes cancer.

- c. *Irvin-Barnwell EA, Benson KM, Lu M et al. Environmental Toxins Found Historically in the Polycythemia Vera Cluster Area and their Potential for Inducing DNA Damage. J Environ Anal Toxicol 2021;8(1):10.4172/2161-0525.1000551.*

This study evaluated the potential for 18 environmental contaminants, including benzene, methylene chloride, and trichloroethylene, to induce DNA damage using the Comet assay, with hematopoietic stem-cell derived progenitor cells. The contaminants were previously detected in an area where a cluster of polycythemia vera (PV) patients existed in northeast Pennsylvania near several hazardous waste sites. Benzene, methylene chloride, and trichloroethylene induced a significant amount of DNA damage in hematopoietic cells compared to the control. Benzene and methylene chloride induced significant effects at the 10 nM concentration and TCE at 100 nM. A dose-dependent relationship for benzene, methylene chloride, and trichloroethylene and DNA damage was found.

Petitioner's Assessment: This study, which found that trichloroethylene induced DNA damage in hematopoietic cells, provides additional support for the genotoxicity of trichloroethylene, a key characteristic of carcinogens.

4. Reviews

- a. *De Guzman K, Stone G, Yang AR et al. Drinking Water and the Implications for Gender Equity and Empowerment: A Systematic Review of Qualitative and Quantitative Evidence. Int J Hygiene Environ Health 2022;247:114044.*

This systematic review of literature between 1980 and 2019 examined drinking water exposures and management and implications for gender equity and empowerment (GEE). The authors conclude that women experienced higher rates of certain diseases/adverse outcomes when exposed to certain contaminants in drinking water compared to men, including breast cancer due to trichloroethylene and arsenic.

Petitioner's Assessment: This review reinforces the evidence that trichloroethylene causes cancer.

- b. *Micallef CM, Charvat H, Houot M-T et al. Estimated Number of Cancers Attributable to Occupational Exposures in France in 2017: An Update Using a New Method for Improved Estimates. J Exposure Sci Environ Epi 2023;33:125-131.*

In this analysis (also described under benzene), population-level prevalence of lifetime exposure to ten carcinogens, including benzene and trichloroethylene, and two occupational circumstances were estimated using the French Census linked with job-exposure matrices and French occupational surveys. Lifetime prevalence of exposure was defined as the proportion of the population alive in 2017 ever exposed to an agent over the defined

exposure period. The population attributable fraction estimates the contribution of a risk factor in the occurrence of a disease at the population level and reflects both the prevalence of the exposure and the magnitude of the association between the risk factor and the outcome. For trichloroethylene and kidney cancer in men, the authors reported an estimated lifetime prevalence over 1967-2007 of 3.7, a population attributable fraction of 1.1 (95% CI: 0.6-1.9), the number of incident cases as 9524, and the number of attributable cases as 109 (95% CI: 56-181). For women, the estimates were 1.2, 0.3 (95% CI: 0.2-0.6), 4954, and 17 (95% CI: 9-30), respectively.

Petitioner's Assessment: This analysis is consistent with the evidence that occupational exposure to trichloroethylene causes cancer, specifically kidney cancer.

- c. *Golka K, Böthig R, Weistenhöfer W et al. Occupation-related cancer in urology – Current Knowledge Including Environmental Medical Aspects. Urologie 2022;61(11):1198-1207. [Abstract in English, article in German].*

The article discusses that renal cell cancer after high exposure to TCE is one of several occupation-related cancers in the field of urology. We were only able to review the abstract as the article is in German.

Petitioner's Assessment: This review appears to reinforce the evidence that trichloroethylene causes cancer.

- d. *Jung K, Khan A, Mocharnuk R et al. Clinical Encounter with Three Cancer Patients Affected by Groundwater Contamination at Camp Lejeune: A Case Series and Review of the Literature. J Med Case Reports 2022;16:272.*

This article includes a review of epidemiological studies for benzene and trichloroethylene as well as on health effects of water contamination in Camp Lejeune. It also presents three cases of cancer patients who lived at Camp Lejeune, a US Marine Corps Base Camp in North Carolina at which several chemical carcinogens, including benzene and trichloroethylene were detected in the camp's water system. The first is a Caucasian man diagnosed with T Cell acute lymphoblastic leukemia at age 37; the second is a Caucasian male who had multiple types of cancer in the prostate, lung, and colon as well as chronic lymphocytic leukemia in his 60s and 70s; and the third is a Caucasian man with recurrent skin cancers including basal cell carcinoma, squamous cell carcinoma, and melanoma from his 50s to 70s. The authors hope to raise awareness about the history of Camp Lejeune's water contamination among cancer care providers and the importance of chemical carcinogens in the environment.

Petitioner's Assessment: This review reinforces the evidence that trichloroethylene causes cancer.

- e. *Georgakopoulou R, Fiste O, Sergeantanis TN et al. Occupational Exposure and Multiple Myeloma Risk: An Updated Review of Meta-Analyses. J Clin Med 2021;10: 4179.*

This review summarizes and critically comments on the evidence across published meta-analyses about the association between occupational exposure and risk of multiple myeloma (MM). Overall, results from eleven meta-studies underscore a statistically significant increased risk for MM among firefighters, hairdressers, and employees exposed to engine exhaust, whereas farming and methylene chloride exposure have been non-significantly

correlated with MM. The results from two meta-analyses, one of seven cohort studies and a more recent one of nine cohort and two case-control studies did not support associations between occupational TCE exposure and MM risk.

Petitioner's Assessment: This review did not support an association between occupational exposure to trichloroethylene and multiple myeloma.

- f. *Odutola MK, Benke G, Fritschi L et al. A Systematic Review and Meta-Analysis of Occupational Exposures and Risk of Follicular Lymphoma. Environ Res 2021;197:110887.*

Researchers identified 58 eligible studies examining the relationship between follicular lymphoma (FL), a common non-Hodgkin lymphoma subtype, and a variety of occupational exposures, including trichloroethylene and benzene. Previous meta-analyses of trichloroethylene (and certain other occupational exposures) have found a positive relationship with non-Hodgkin lymphoma without stratification by subtype. A positive association between FL and exposure to chlorinated solvents, including carbon tetrachloride, chloroform, dichloroethane, dichloromethane, methyl chloride, and TCE, was observed (meta-RR=1.35, 95%CI = 1.09,1.68), based on five case control studies (143/792 cases exposed). Two studies investigated TCE (75/1236 cases exposed). A pooled analysis of case-control studies from six European countries reported a significant 2-fold increased FL risk with high intensity exposure to trichloroethylene, but no significant trend with increasing duration or cumulative dose was observed.

Petitioner's Assessment: This review provides some support for the association between trichloroethylene and follicular lymphoma.

Appendix 4: Requested Changes to Food Additive Regulations

Part 1: Requested changes to 21 CFR § 172.560

TITLE 21--FOOD AND DRUGS CHAPTER
I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER
B--FOOD FOR HUMAN CONSUMPTION (CONTINUED)
PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR
HUMAN CONSUMPTION

Subpart F--Flavoring Agents and Related Substances

Sec. 172.560 Modified hop extract

The food additive modified hop extract may be safely used in beer in accordance with the following prescribed conditions:

- (a) The food additive is used or intended for use as a flavoring agent in the brewing of beer.
- (b) The food additive is manufactured by one of the following processes:
 - (1) The additive is manufactured from a hexane extract of hops by simultaneous isomerization and selective reduction in an alkaline aqueous medium with sodium borohydride, whereby the additive meets the following specifications:
 - (i) A solution of the food additive solids is made up in approximately 0.012 n alkaline methyl alcohol (6 milliliters of 1 n sodium hydroxide diluted to 500 milliliters with methyl alcohol) to show an absorbance at 253 millimicrons of 0.6 to 0.9 per centimeter. (This absorbance is obtained by approximately 0.03 milligram solids per milliliter.) The ultraviolet absorption spectrum of this solution exhibits the following characteristics: An absorption peak at 253 millimicrons; no absorption peak at 325 to 330 millimicrons; the absorbance at 268 millimicrons does not exceed the absorbance at 272 millimicrons.
 - (ii) The boron content of the food additive does not exceed 310 parts per million (0.0310 percent), calculated as boron.
 - (2) The additive is manufactured from hops by a sequence of extractions and fractionations, using ~~benzene~~, light petroleum spirits, and methyl alcohol as solvents, followed by isomerization by potassium carbonate treatment. Residues of solvents in the modified hop extract shall not exceed ~~1.0 part per million of benzene~~, 1.0 part per million of light petroleum spirits, and 250 parts per million of methyl alcohol. The light petroleum spirits ~~and benzene solvents~~ shall comply with the specifications in § 172.250 except that the boiling point range for light petroleum spirits is 150 deg.F-300 deg.F.
 - (3) The additive is manufactured from hops by a sequence of extractions and fractionations, using ~~methylene chloride~~, hexane, and methyl alcohol as solvents, followed by isomerization by sodium hydroxide treatment. Residues of the solvents in the modified hop extract shall not exceed ~~5 parts per million of methylene chloride~~, 25 parts per million of hexane, and 100 parts per million of methyl alcohol.
 - (4) The additive is manufactured from hops by a sequence of extractions and fractionations, using

~~benzene~~, light petroleum spirits, methyl alcohol, n- butyl alcohol, and ethyl acetate as solvents, followed by isomerization by potassium carbonate treatment. Residues of solvents in the modified hop extract shall not exceed ~~1.0 part per million of benzene~~, 1.0 part per million of light petroleum spirits, 50 parts per million of methyl alcohol, 50 parts per million of n- butyl alcohol, and 1 part per million of ethyl acetate. The light petroleum spirits ~~and benzene solvents~~ shall comply with the specifications in § 172.250 except that the boiling point range for light petroleum spirits is 150 deg.F to 300 deg.F.

~~(5) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the following solvents: Ethylene dichloride, hexane, isopropyl alcohol, methyl alcohol, methylene chloride, trichloroethylene, and water; followed by isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene and a further sequence of extractions and fractionations using one or more of the solvents set forth in this paragraph. Residues of the solvents in the modified hop extract shall not exceed 125 parts per million of hexane; 150 parts per million of ethylene dichloride, methylene chloride, or trichloroethylene; or 250 parts per million of isopropyl alcohol or methyl alcohol.~~

~~(6) The additive is manufactured from hops by an initial extraction and fractionation using one or more of the solvents listed in paragraph (b)(5) of this section followed by: Hydrogenation using palladium as a catalyst in methyl alcohol, ethyl alcohol, or isopropyl alcohol acidified with hydrochloric or sulfuric acid; oxidation with peracetic acid; isomerization by calcium chloride or magnesium chloride treatment in ethylene dichloride, methylene chloride, or trichloroethylene (alternatively, the hydrogenation and isomerization steps may be performed in reverse order); and a further sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section. The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section.~~

~~(7) The additive is manufactured from hops as set forth in paragraph (b)(6) of this section followed by reduction with sodium borohydride in aqueous alkaline methyl alcohol, and a sequence of extractions and fractionations using one or more of the solvents listed in paragraph (b)(5) of this section. The additive shall meet the residue limitations as prescribed in paragraph (b)(5) of this section, and a boron content level not in excess of 300 parts per million (0.0300 percent), calculated as boron.~~

~~(8)(5) The additive is manufactured from hops as a nonisomerizable nonvolatile hop resin by an initial extraction and fractionation using one or more of the following solvents: hexane, isopropyl alcohol, methyl alcohol, and water, listed in paragraph (b)(5) of this section followed by a sequence of aqueous extractions and removal of nonaqueous solvents to less than 0.5 percent. The additive is added to the wort before or during cooking in the manufacture of beer.~~

Part 2: Requested changes to 21 CFR § 172.710

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR
HUMAN CONSUMPTION (CONTINUED)
PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN
CONSUMPTION

Subpart H—Other Specific Usage Additives

Sec. 172.710 Adjuvants for pesticide use dilutions.

The following surfactants and related adjuvants may be safely added to pesticide use dilutions by a grower or applicant prior to application to the growing crop:

- n- Alkyl (C8-C18) amine acetate, where the alkyl groups (C8-C18) are derived from coconut oil, as a surfactant in emulsifier blends at levels not in excess of 5 percent by weight of the emulsifier blends that are added to herbicides for application to corn and sorghum.
- Di-n- alkyl (C8-C18) dimethyl ammonium chloride, where the alkyl groups (C8-C18) are derived from coconut oil, as surfactants in emulsifier blends at levels not in excess of 5 percent by weight of emulsifier blends that are added to herbicides for application to corn or sorghum.
- Diethanolamide condensate based on a mixture of saturated and unsaturated soybean oil fatty acids (C16-C18) as a surfactant in emulsifier blends that are added to the herbicide atrazine for application to corn.
- Diethanolamide condensate based on stripped coconut fatty acids (C10 C18) as a surfactant in emulsifier blends that are added to the herbicide atrazine for application to corn.
- [alpha]-(p- Dodecylphenyl)-omega- hydroxypoly (oxyethylene) produced by the condensation of 1 mole of dodecylphenol (dodecyl group is a propylene tetramer isomer) with an average of 4-14 or 30-70 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-70.
- ~~Ethylene dichloride.~~
- Polyglyceryl phthalate ester of coconut oil fatty acids.
- [alpha]-[p- (1,1,3,3-Tetramethylbutyl) phenyl]-omega- hydroxypoly(oxyethylene) produced by the condensation of 1 mole of p- (1,1,3,3-tetramethylbutyl) phenol with an average of 4-14 or 30-70 moles of ethylene oxide; if a blend of products is used, the average number of moles of ethylene oxide reacted to produce any product that is a component of the blend shall be in the range of 4-14 or 30-70.
- [alpha]-[p- (1,1,3,3-Tetramethylbutyl) phenyl]-omega- hydroxypoly(oxyethylene) produced by the condensation of 1 mole of p- (1,1,3,3-tetramethylbutyl) phenol with 1 mole of ethylene oxide.
- Sodium acrylate and acrylamide copolymer with a minimum average molecular weight of 10,000,000 in which 30 percent of the polymer is comprised of acrylate units and 70 percent acrylamide units, for use as a drift control agent in herbicide formulations applied to crops at a level not to exceed 0.5 ounces of the additive per acre.

Part 3: Requested changes to 21 CFR § 173.230

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR
HUMAN CONSUMPTION (CONTINUED)
[PART 173 – SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN
CONSUMPTION](#)

Subpart C—Solvents, Lubricants, Release Agents and Related Substances

~~Sec. 173.230 Ethylene dichloride.~~

~~A tolerance of 30 parts per million is established for ethylene dichloride in spice oleoresins when present therein as a residue from the extraction of spice; *Provided, however,* That if residues of other chlorinated solvents are also present the total of all residues of such solvents shall not exceed 30 parts per million.~~

Part 4: Requested changes to 21 CFR § 173.255

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR
HUMAN CONSUMPTION (CONTINUED)
[PART 173 – SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN
CONSUMPTION](#)

Subpart C—Solvents, Lubricants, Release Agents and Related Substances

~~Sec. 173.255 Methylene chloride.~~

~~**methylene chloride** may be present in food under the following conditions:~~

- ~~(a) In spice oleoresins as a residue from the extraction of spice, at a level not to exceed 30 parts per million; *Provided,* That, if residues of other chlorinated solvents are also present, the total of all residues of such solvents shall not exceed 30 parts per million.~~
- ~~(b) In hops extract as a residue from the extraction of hops, at a level not to exceed 2.2 percent, *Provided,* That:
 - ~~(1) The hops extract is added to the wort before or during cooking in the manufacture of beer.~~
 - ~~(2) The label of the hops extract identifies the presence of the **methylene chloride** and provides for the use of the hops extract only as prescribed by paragraph (b)(1) of this section.~~~~
- ~~(c) In coffee as a residue from its use as a solvent in the extraction of caffeine from green coffee beans, at a level not to exceed 10 parts per million (0.001 percent) in decaffeinated roasted coffee and in decaffeinated soluble coffee extract (instant coffee).~~

Part 5: Requested changes to 21 CFR § 173.290

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR
HUMAN CONSUMPTION (CONTINUED)
PART 173 – SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN
CONSUMPTION

Subpart C—Solvents, Lubricants, Release Agents and Related Substances

~~Sec. 173.290 Trichloroethylene.~~

~~Tolerances are established for residues of trichloroethylene resulting from its use as a solvent in the manufacture of foods as follows:~~

Decaffeinated ground- coffee	25 parts per million.
Decaffeinated soluble- (instant) coffee extract	10 parts per million.
Spice oleoresins	30 parts per million (provided that if residues of other chlorinated solvents are also present, the total of all residues of such solvents in spice oleoresins shall not exceed 30 parts per million).

Part 6: Requested changes to 21 CFR § 173.315(a)(4)

TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER B--FOOD FOR
HUMAN CONSUMPTION (CONTINUED)
PART 173 – SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN
CONSUMPTION

Subpart D—Specific Usage Additives

Sec. 173.315 Chemicals used in washing or to assist in the peeling of fruits and vegetables.

Chemicals may be safely used to wash or to assist in the peeling of fruits and vegetables in accordance with the following conditions:

(a) The chemicals consist of one or more of the following:

[...]

(4) Substances identified in this paragraph (a)(4) for use in flume water for washing sugar beets prior to the slicing operation and subject to the limitations as are provided for the level of the substances in the flume water:

Substance	Limitations
[alpha]-Alkyl-omega-hydroxypoly-(oxyethylene) produced by condensation of 1 mole of C11-C486315 straight chain randomly substituted secondary alcohols with an average of 9 moles of ethylene oxide	Not to exceed 3 ppm.
Linear undecylbenzenesulfonic acid	Do.
Dialkanolamide produced by condensing 1 mole of methyl laurate with 1.05 moles of diethanolamine	Not to exceed 2 ppm.

Triethanolamine	Do.
Ethylene glycol monobutyl ether	Not to exceed 1 ppm.
Oleic acid conforming with § 172.860 of this chapter	Do.
Tetrapotassium pyrophosphate	Not to exceed 0.3 ppm.
Monoethanolamine	Do.
Ethylene dichloride	Not to exceed 0.2 ppm.
Tetrasodium ethylenediaminetetraacetate	Not to exceed 0.1 ppm.

Appendix 5 List of References

A. References in Cover Letter Portion of Petition

1. Seasoning and Spice Association. Glossary. <https://seasoningandspice.org.uk/faq-glossary>.
2. Water Only Processing. <https://www.swisswater.com/>.
3. Clean Label Project. More Methylene Chloride! April 2023. https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper_3_2.pdf.
4. Clean Label Project. Decaf Coffee: Our Point of View. 2020. <https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper.pdf>.
5. Clean Label Project. Are There Chemicals in Your Decaffeinated Coffee? 2023. <https://cleanlabelproject.org/are-there-chemicals-in-your-decaffeinated-coffee/>.
6. Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. J Agric Food Chem 2003; 51:8120-8127,
7. FDA. Questions and Answers on the Occurrence of Benzene in Soft Drinks and Other Beverages. Content current as of 2/25/22. <https://www.fda.gov/food/environmental-contaminants-food/questions-and-answers-occurrence-benzene-soft-drinks-and-other-beverages>.
8. FDA. Data on Benzene in Soft Drinks and Other Beverages. Last updated on 3/25/2015. <http://wayback.archive-it.org/7993/20161022184011/http://www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm055815.htm>.
9. Lachenmeier DW, Reusch H, Sproll C et al. Occurrence of Benzene as a Heat-Induced Contaminant of Carrot Juice for Babies in a General Survey of Beverages. Food Add Contam 2008;25(10):1216-1224.
10. Public Citizen v. Young, 831 F.2d 1108, 1122 (D.C. Cir. 1987).
11. Les v. Reilly, 968 F.2d 985, 989 (9th Cir. 1992)
12. EPA TRI Explorer, 2021 National Analysis Dataset, Releases: Facility Report for Benzene, 2021. https://enviro.epa.gov/triexplorer/release_fac?p_view=USFA&trilib=TRIQ2&sort=RE_TOLBY&sort_fmt=2&state=All+states&county=All+counties&chemical=0000071432&industry=311&industry=3121&year=2021&tab_rpt=1&fld=RELLBY&fld=TSFDSP
13. FDA. FDA Alerts Drug Manufacturers to the Risk of Benzene Contamination in Certain Drugs. Content current as of 12/23/2022. <https://www.fda.gov/drugs/pharmaceutical-quality-resources/fda-alerts-drug-manufacturers-risk-benzene-contamination-certain-drugs> .
14. FDA, Q3C – Tables and List; Guidance for Industry. 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q3c-tables-and-list-rev-4>.
15. FDA. Center for Drug Evaluation and Research. Office of Pharmaceutical Quality. Manual of Policies and Procedures. Acceptance Criteria for Residual Solvents. 2022. <https://www.fda.gov/media/75126/download>.
16. FDA. Appendix 4: Toxicological Data for Class 1 Solvents (no date, draft 7). <https://www.fda.gov/media/71738/download>.
17. ICH Guideline Q3C (R6) on Impurities – Support Document 1: Toxicological Data for Class I Solvents. European Medicines Agency, October 2018. at https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-q3c-r6-impurities-support-document-1-toxicological-data-class-1-solvents-step-5_en.pdf.
18. NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity (CAS No. 107-06-2), Technical Report Series No. 55, 1978. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055/index.html>.
19. NTP, Report on Carcinogens, Fifteenth Edition, 2021. Last updated April 14, 2023. See

- <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html>.
20. IARC, Preamble to the IARC Monographs (amended January 2019)
<https://monographs.iarc.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/>
 21. IARC, Mission, accessed April 18, 2023, <https://www.iarc.who.int/iarc-mission/>.
 22. The President's Cancer Panel, Reducing Environmental Cancer Risk: What We Can Do Now, 2008-2009 Annual Report of the President's Cancer Panel, 2010.
https://deainfo.nci.nih.gov/advisory/pcp/annualReports/pcp08-09rpt/PCP_Report_08-09_508.pdf.
 23. EPA. National Primary Drinking Water Regulations. Last updated on January 9, 2023.
<https://www.epa.gov/ground-water-and-drinking-water/national-primary-drinking-water-regulations#Organic>.
 24. ATSDR. Toxicological Profile for Benzene. 2007.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.
 25. ATSDR Toxicological Profile for Methylene Chloride. 2000.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
 26. ATSDR. Toxicological Profile for Trichloroethylene. 2019.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>
 27. ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.
 28. ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
 29. OEHHA, Proposition 65, accessed on April 18, 2023, at
<http://www.oehha.ca.gov/prop65.html>.
 30. American Cancer Society. Known and Probable Human Carcinogens. Last revised July 8, 2022. <https://www.cancer.org/cancer/risk-prevention/understanding-cancer-risk/known-and-probable-human-carcinogens.html>.
 31. World Health Organization. 10 Chemicals of Public Health Concern. 2020.
<https://www.who.int/news-room/photo-story/photo-story-detail/10-chemicals-of-public-health-concern>.
 32. World Health Organization. Evaluation of Certain Food Additives. Twenty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. Technical Report Series 648, 1980.
https://apps.who.int/iris/bitstream/handle/10665/41403/WHO_TRS_648.pdf;jsessionid=35B181F8B1C12C4DD441B240A6E1CCE9?sequence=1.
 33. Salviano dos Santos VP, Salgado AM, Torres AG, Pereira KS. Benzene as a Chemical Hazard in Processed Foods. *Int J Food Sci* 2015;2015:545640.
 34. EPA. Initial List of Hazardous Air Pollutants with Modifications. Last updated on December 19, 2022. <https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications>.
 35. EPA. Hazardous Air Pollutants. Last updated on February 9, 2023.
<https://www.epa.gov/haps>.
 36. EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health (Last updated January 9, 2023) <https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-human-health>.
 37. Final Risk Evaluation for Methylene Chloride (Last updated on April 20, 2023).
<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-methylene-chloride> and https://www.epa.gov/system/files/documents/2022-11/MC_Final%20Revised%20RD_10.26.22-final%20%281%29.pdf.
 38. Risk Evaluation for 1,2-Dichloroethane (Last updated on May 25, 2023).
<https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-12->

- [dichloroethane](#).
39. EPA. Final Scope of the Risk Evaluation for 1,2-Dichloroethane. August 2020. https://www.epa.gov/sites/default/files/2020-09/documents/casrn_107-06-2_12-dichloroethane_final_scope.pdf.
 40. EPA. Risk Management for Methylene Chloride. Updated June 7, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-management-methylene-chloride>.
 41. EPA. Biden-Harris Administration Proposes Ban on Trichloroethylene to Protect Public from Toxic Chemical Known to Cause Serious Health Risks. October 23, 2023. <https://www.epa.gov/newsreleases/biden-harris-administration-proposes-ban-trichloroethylene-protect-public-toxic>.
 42. EPA. Integrated Risk Information System (IRIS) Glossary. Last updated 1/27/2023. https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywords/search.do;jsessionid=VYQEuB3zwOSBOnnxbuUp7aYNm18mPOKW8YyMXjY6P_kKAGKsVS5F!-1457352436?details=&vocabName=IRIS%20Glossary&filterTerm=Reference%20dose&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=Reference%20dose&filterMatchCriteria=Contains.
 43. EPA. IRIS. Benzene. Last updated 04/17/2003. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=276.
 44. EPA. IRIS Chemical Assessment Summary. Benzene. Last revised 04/17/2003. https://iris.epa.gov/static/pdfs/0276_summary.pdf.
 45. EPA. IRIS. Dichloromethane. Last updated 11/18/2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nمبر=70.
 46. EPA. IRIS. Chemical Assessment Summary. Dichloromethane. Last revised 11/18/2011. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0070_summary.pdf.
 47. EPA. IRIS. Trichloroethylene. Last updated 9/28/2011. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=199.
 48. EPA. IRIS. Chemical Assessment Summary. Trichloroethylene. Last revised 9/28/2011. https://iris.epa.gov/static/pdfs/0199_summary.pdf.
 49. EPA. IRIS. 1,2-Dichloroethane. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=149.
 50. ATSDR. Minimal Risk Levels (MRLs) for Hazardous Substances. Last reviewed 6/21/2018. <https://www.atsdr.cdc.gov/mrls/index.html>.
 51. Dorsey ER, Zafar M, Lettenberger SE et al. Trichloroethylene: An Invisible Cause of Parkinson's Disease? J Parkinson's Disease 2023;13:203-218.

B. Additional References in Appendix 1

Benzene

1. IARC. Benzene, IARC Monograph – Volume 120, 2018, p. 297. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Benzene-2018>.
2. ATSDR. Addendum to the Toxicological Profile for Benzene. 2015. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=40&tid=14>.
3. NTP. NTP Genetically Modified Model Report on the Toxicology and Carcinogenesis Studies of Benzene (CASRN 71-43-2) in Genetically Modified Haploinsufficient p16ink4a/p19Arf Mice (Gavage Study), NTP GMM 8, NIH Publication No. 08-4425, 2007. <https://ntp.niehs.nih.gov/publications/reports/gmm/gmm08>.
4. OEHHA. Proposition 65. Benzene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/benzene>.

5. NTP. Toxicology and Carcinogenesis Studies of Benzene (CAS No. 71-43-2) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No. 289, 1986. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr289.pdf.
6. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Benzene, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/benzene.pdf>.

Ethylene Dichloride

7. IARC. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide (Part 1, Part 2, Part 3) – Volume 71, 1999, p. 522. <https://publications.iarc.fr/89>. [Includes 1,2-Dichloroethane.]
8. OEHHA. Proposition 65. Ethylene Dichloride (1,2-Dichloroethane). 2023. <https://oehha.ca.gov/proposition-65/chemicals/ethylene-dichloride-12-dichloroethane>.
9. HHS, NTP. Report on Carcinogens, Fifteenth Edition, 1,2-Dichloroethane, 2021. <https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/dichloroethane.pdf>.

Methylene Chloride

10. IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 243. [Includes methylene chloride.] <https://publications.iarc.fr/547>.
11. OEHHA. Proposition 65. Dichloromethane (Methylene Chloride), 2023. <https://oehha.ca.gov/proposition-65/chemicals/dichloromethane-methylene-chloride>.
12. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Dichloromethane, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloromethane.pdf>.
13. NTP. Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). Technical Report Series No. 306, 1986. <https://ntp.niehs.nih.gov/publications/reports/tr/300s/tr306/index.html>.

Trichloroethylene

14. EPA. Risk Evaluation for Trichloroethylene. Last updated on June 15, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-trichloroethylene-and> https://www.epa.gov/sites/default/files/2020-11/documents/1_risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf.
15. EPA. Toxicological Review of Trichloroethylene. EPA/635/R-09/011F, 2011. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf.
16. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Trichloroethylene, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/trichloroethylene.pdf>.
17. HHS, NTP. Report on Carcinogens Monograph on Trichloroethylene. RoC Monograph 05. 2015. https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/monographs/finaltce_508.pdf
18. IARC. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. Volume 106. 2014. <https://publications.iarc.fr/130>.
19. OEHHA. Proposition 65, Trichloroethylene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/trichloroethylene>.
20. NTP. Carcinogenesis Studies of Trichloroethylene (Without Epichlorohydrin) (CAS No. 79-01-6) in F344/N Rats and B6C3F1 Mice (Gavage Studies), Technical Report Series No.243, 1990 <https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr243/index.html>.
21. NTP. Toxicology and Carcinogenesis Studies of Trichloroethylene (CAS No. 79-01-6) in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies), Technical Report Series No.273, 1988. <https://ntp.niehs.nih.gov/publications/reports/tr/200s/tr273/index.html>.
22. NTP. Carcinogenesis Bioassay of Trichloroethylene (CAS No. 79-01-6), Technical Report

Series No. 2, 1976. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr002/index.html>.

C. Additional References in Appendix 2

1. National Library of Medicine. PubChem. Benzene. <https://pubchem.ncbi.nlm.nih.gov/compound/241>.
2. National Library of Medicine. PubChem. Ethylene Dichloride. <https://pubchem.ncbi.nlm.nih.gov/compound/11>.
3. National Library of Medicine. PubChem. Methylene Chloride. <https://pubchem.ncbi.nlm.nih.gov/compound/6344>.
4. National Library of Medicine. PubChem. Trichloroethylene. <https://pubchem.ncbi.nlm.nih.gov/compound/6575>.
5. FDA. Substances Added to Food (formerly EAFUS). Benzene. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/?set=FoodSubstances&id=BENZENE&sort=Sortterm_ID&order=ASC&startrow=1&type=basic&search=benzene.
6. FDA. Substances Added to Food (formerly EAFUS). Ethylene Dichloride. https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=ETHYLENEDICHLORIDE&sort=Sortterm_ID&order=ASC&startrow=1&type=basic&search=ethylene%20dichloride.
7. FDA. Substances Added to Food (formerly EAFUS). Methylene Chloride. <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=METHYLENECHLORIDE>.
8. FDA. Substances Added to Food (formerly EAFUS). Trichloroethylene. <https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=FoodSubstances&id=TRICHLOROETHYLENE>.
9. FDA. FDA's Global Substance Registration System. Benzene. <https://precision.fda.gov/uniisearch/srs/unii/J64922108F>.
10. FDA. FDA's Global Substance Registration System. Ethylene Dichloride. <https://precision.fda.gov/uniisearch/srs/unii/551631JI47>.
11. FDA. FDA's Global Substance Registration System. Methylene Chloride. <https://precision.fda.gov/uniisearch/srs/unii/588X2YUY0A>.
12. FDA. FDA's Global Substance Registration System. Trichloroethylene. <https://precision.fda.gov/uniisearch/srs/unii/290YE8AR51>.
13. ChemEurope. Decaffeination. <https://www.chemeuropa.com/en/encyclopedia/Decaffeination.html>.

D. Additional References in Appendix 3 Parts 1-3

Part 1

1. FDA. Drug Recalls. Content current as of June 14, 2023. <https://www.fda.gov/drugs/drug-safety-and-availability/drug-recalls>.
2. FDA. FDA Updates on Hand Sanitizers Consumers Should Not Use. 2021. <https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-hand-sanitizers-consumers-should-not-use>.
3. FDA. Interim Response Letter from FDA to Valisure LLC dated November 19, 2021. <https://www.regulations.gov/document/FDA-2021-P-0497-0005>.
4. Starbucks. What are the Sizes of Starbucks Drinks? 2022. <https://customerservice.starbucks.com/sbux?id=topics&article=KB0011498>.
5. Clean Label Project. Are There Chemicals in Your Decaffeinated Coffee? 2023. <https://cleanlabelproject.org/are-there-chemicals-in-your-decaffeinated-coffee/>.
6. Letter from James C. Wallwork, Division of Petition Review, FDA Office of Food Additive Safety, to Sidney M. Wolfe, Director, Public Citizen Health Research Group, November 1, 2010. <https://www.regulations.gov/document/FDA-1975-P-0006-0008>.

Part 2

7. NTP. History of the Report on Carcinogens. <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/history>.
8. NTP. Fifteenth Report on Carcinogens, 2021. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc>.
9. NTP. Fifteenth Report on Carcinogens, 2021, p. 6. Last updated April 14, 2023. See https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/introduction_508.pdf.
10. NTP. History & Milestones. <https://ntp.niehs.nih.gov/howeare/history>.
11. NTP. Organization. <https://ntp.niehs.nih.gov/howeare/organization>.
12. NTP. Cancer Evaluation Criteria. 2023. <https://ntp.niehs.nih.gov/whatwestudy/testpgm/cartox/criteria>.
13. IARC. IARC Monographs – General Information. <https://monographs.iarc.who.int/home/iarc-monographs-general-information/>.
14. IARC. Monographs available. <https://monographs.iarc.who.int/monographs-available/>.
15. OEHHA. How chemicals are added to the Proposition 65 list, 2023. <https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list>.
16. OEHHA. Proposition 65 in Plain Language, 2023. <http://www.oehha.ca.gov/prop65/background/p65plain.html>.
17. OEHHA. Proposition 65, Carcinogen Identification Committee, 2023. Undated. <https://oehha.ca.gov/proposition-65/carcinogen-identification-committee>.
18. EPA. EPA History. Last updated on April 17, 2023. <https://www.epa.gov/history>.
19. EPA. Basic Information about the Integrated Risk Information System. Last updated on May 18, 2023. <https://www.epa.gov/iris/basic-information-about-integrated-risk-information-system>.
20. EPA. Risk Evaluations for Existing Chemicals under TSCA. Last updated February 24, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluations-existing-chemicals-under-tsca>.
21. EPA. Chemicals Undergoing Risk Evaluation under TSCA. Last updated on June 8, 2023. <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/chemicals-undergoing-risk-evaluation-under-tsca>.
22. EPA. Nontechnical Summary of the Risk Evaluation for Methylene Chloride. June 2020. https://19january2021snapshot.epa.gov/sites/static/files/2020-06/documents/mc_final_re_nontechnical_summary.pdf.
23. EPA. How EPA Regulates Drinking Water Contaminants. Last Updated November 2, 2022. <https://www.epa.gov/sdwa/how-epa-regulates-drinking-water-contaminants>.
24. ATSDR. <https://www.atsdr.cdc.gov/>. Last updated May 10, 2023.

Part 3

25. IARC. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Halogenated Hydrocarbons. Volume 20, 1979, <https://publications.iarc.fr/38>.
26. EPA. Risk Evaluation for Methylene Chloride (Dichloromethane, DCM). EPA Document# EPA-740-RI-8010, June 2020, pp. 290-293. https://www.epa.gov/sites/default/files/2020-06/documents/1_mecl_risk_evaluation_final.pdf.
27. IARC. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volume 1 to 42. 1987, p. 62, 194. <https://publications.iarc.fr/139>.
28. Aiso S, Take M, Kasai T, et al. Inhalation carcinogenicity of dichloromethane in rats and mice. *Inhal Toxicol* 2014;26(8):435-451. <https://doi.org/10.3109/08958378.2014.905660>.
29. NTP. Technical Report Series No. 426. Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin in Male F344/N Rats As Vehicles for Gavage. 1994.

- <https://ntp.niehs.nih.gov/publications/reports/tr/400s/tr426>.
30. EPA. Final Risk Evaluation for Trichloroethylene. December 2022. P. 8.
https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf.
 31. EPA, Risk Evaluation for Trichloroethylene, EPA Document #740R18008, 2020, p. 251.
https://www.epa.gov/sites/default/files/2020-11/documents/1_risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf.
 32. IARC. Cadmium, nickel, some epoxides, miscellaneous industrial chemicals and general considerations on volatile anaesthetics. Volume 11, 1976. P. 271.
<https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Cadmium-Nickel-Some-Epoxides-Miscellaneous-Industrial-Chemicals-And-General-Considerations-On-Volatile-Anaesthetics-1976>.

E. Additional References in Appendix 3 Part 4 (Literature Search)

1. Boyle J, Ward MH, Cerhan JR et al. Modeling Historic Environmental Pollutant Exposures and Non-Hodgkin Lymphoma Risk. *Environ Res* 2023;224:115506.
2. Malavolti M, Malagoli C, Filippini T et al. Residential Proximity to Petrol Stations and Risk of Childhood Leukemia. *Eur J Epidem* 2023;38:771-782.
3. Nethery RC, Vega S, Frazier AL, Laden F. Mobile Source Benzene Regulations and Risk of Childhood and Young Adult Hematologic Cancers in Alaska: A Quasi-Experimental Study. *Epi* 2023;34:385-388.
4. Goldberg MS, Zapata-Marin S, Labrèche F et al. Ambient Exposures to Selected Volatile Organic Compounds and the Risk of Prostate Cancer in Montreal. *Environ Epi* 2022;6:e231.
5. Dai K, Wang C, Yao W, Hao C. Expression Level and Function Analysis of Serum miRNAs in Workers with Occupational Exposure to Benzene Series. *Chemosphere* 2023;313:137460.
6. Lin D, Wang D, Li P et al. Whole-Exome Sequencing Identified Recurrent and Novel Variants in Benzene-Induced Leukemia. *BMC Med Genomics* 2023;16:13.
7. NIH National Human Genome Research Institute. Exome. Undated.
<https://www.genome.gov/genetics-glossary/Exome>.
8. Lu Y, Sui P, Li J et al. Benzene Metabolite Hydroquinone Enhances Self-Renewal and Proliferation of Preleukemic Cells Through the Ppar γ Pathway. *Toxicol Letters* 2023;382:33-40.
9. Sayed AE-D, Idriss SK, Abdel-Ghaffar SKh, Hussein AAA. Haemato-Biochemical, Mutagenic, and Histopathological Changes in *Oreochromis niloticus* Exposed to BTX. *Environ Sci Pollution Res* 2023;30:59301-59315.
10. Xuan M, Wu Y, Wang H et al. Effect of mir-92a-3p on Hydroquinone Induced Changes in Human Lymphoblastoid Cell Cycle and Apoptosis. *Environ Toxicol* 2023;381420-1430.
11. Yang X, Dong S, Li C et al. Hydroquinone Triggers Pyroptosis and Endoplasmic Reticulum Stress Via AhR-Regulated Oxidative Stress in Human Lymphocytes. *Toxicol Letters* 2023;376:39-50.
12. Phillips RV, Wei L, Cardenas A et al. Epigenome-Wide Association Studies of Occupational Exposure to Benzene and Formaldehyde. *Epigenetics* 2022;17(3):2259-2277.
13. Teschendorff AE, Gao Y, Jones A, et al. DNA Methylation Outliers in Normal Breast Tissue Identify Field Defects that are Enriched in Cancer. *Nat Commun.* 2016;7:10478.
14. Francisco LFV, da Silva RN, Oliverreira MA et al. Occupational Exposures and Risks of Non-Hodgkin Lymphoma: A Meta-Analysis. *Cancers (Basel)* 2023; 15(9):2600.
15. Galatro D, Trigo-Ferre R, Nakashook-Zettler A et al. Framework for Evaluating Potential

- Causes of Health Risk Factors Using Average Treatment Effect and Uplift Modelling. *Algorithms* 2023;16:166.
16. Micallef CM, Charvat H, Houot M-T et al. Estimated Number of Cancers Attributable to Occupational Exposures in France in 2017: An Update Using a New Method for Improved Estimates. *J Exposure Sci Environ Epi* 2023;33:125-131.
 17. Vallée M. How Government Health Agencies Obscure the Impact of Environmental Pollution and Perpetuate Reductionist Framings of Disease: The Case of Leukemia. *Int J Soc Determinants Health Serv* 2023; 27551938231169119.
 18. Yusoff NA, Hamid ZA, Budin SB, Taib IS. Linking Benzene, in Utero Carcinogenicity and Fetal Hematopoietic Stem Cell Niches: A Mechanistic Review. *Int J Mol Sci* 2023;24:6355.
 19. Reddam A, Volz DC. Inhalation of two Prop 65-listed chemicals within vehicles may be associated with increased cancer risk. *Env Int* 2021; 149:106402.
 20. Knox KE, Dodson RE, Rudel RA et al. Identifying Toxic Consumer Products: A Novel Data Set Reveals Air Emissions of Potent Carcinogens, Reproductive Toxicants, and Developmental Toxicants. *Environ Sci Technol* 2023, 57:7454-7465.
 21. Andrew AS, Li M, Shi X et al. Kidney Cancer Risk Associated with Historic Groundwater Trichloroethylene Contamination. *J Environ Res Public Health* 2022;19:618.
 22. Chuang Y-S, Lee C-Y, Lin P-C et al. Breast Cancer Incidence in a National Cohort of Female Workers Exposed to Special Health Hazards in Taiwan: A Retrospective Case-Cohort Study of ~300,000 Occupational Records Spanning 20 Years. *Int Arch Occup Environ Health* 2022;95:1979-1993.
 23. CDC. Standardized Incidence Ratio (SIR): A Math-based Approach to Evaluating Unusual Patterns of Cancer. November 16, 2022. <https://www.cdc.gov/nceh/cancer-environment/pdfs/standardized-incidence-ratio-fact-sheet-508.pdf>.
 24. Weinstein B, Da Silva A, Carpenter DO. Exocrine Pancreatic Cancer and Living Near to Waste Sites Containing Hazardous Organic Chemicals, New York State, USA – An 18-Year Population Study. *Int J Occup Med Environ Health* 2022;35(4):459-471.
 25. Tessema ST, Mahgoub AE, Nakhleh R. Angiosarcoma: A Rare Malignancy Linked to Chemical Exposures. *Cureus* 2022;14(5):e25289.
 26. Li N, Zhai Z, Zheng Y et al. Association of 13 Occupational Carcinogens in Patients with Cancer, Individually and Collectively, 1990-2017. *JAMA Netw Open* 2021;4(2):e2037530.
 27. Purdue MP, Rhee J, Moore L et al. Differences in Risk Factors for Molecular Subtypes of Clear Cell Renal Cell Carcinoma. *Int J Cancer* 2021;149:1448-1454.
 28. Pedersen JE, Strandberg-Larsen K, Andersson M, Hansen J. Occupational Exposure to Specific Organic Solvents and Risk of Subtypes of Breast Cancer in a Large Population of Danish Women, 1964-2016. *Occup Environ Med* 2020;78:192-198.
 29. Lynge E, Kaerlev L, Olsen J et al. Rare Cancers of Unknown Etiology: Lessons Learned from a European Multi-Center Case-Control Study. *Eur J Epidemiol* 2020;35:937-948.
 30. Abdrahoh ME, El-Missiry MA, Othman AI et al. Constant Light Exposure and/or Pinealectomy Increases Susceptibility to Trichloroethylene-Induced Hepatotoxicity and Liver Cancer in Male Mice. *Environ Sci Pollut Res* 2022;29:60371-60384.
 31. Thapa R, Wilson GD. The Importance of CD44 as a Stem Cell Biomarker and Therapeutic Target in Cancer. *Stem Cells Int* 2016;2016:2087204.
 32. Li SP, Chang QQ, Ren XH et al. Induction of Hepatocellular Carcinoma in B6C3(F1) Mice Chronically Exposed to Trichloroethylene with Enhanced Acetylation of Histone H2AK9ac and SET Expression in the Liver Tissue. *Chinese J Industrial Hygiene Occup Dis [Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi]* 2021;39(12):910-914. [article in Chinese]
 33. Bayarkhangai B, Noureldin S, Yu L et al. A Comprehensive and Perspective View of Oncoprotein SET in Cancer. *Cancer Med* 2018;7(7):3084-3094.
 34. NIH National Center for Biotechnology Information. HDAC1 histone deacetylase 1.

- <https://www.ncbi.nlm.nih.gov/gene/3065>.
35. Hosgood HD, Rahman ML, Blansky D et al. Targeted proteomic scan identifies alteration of serum proteins among workers occupationally exposed to low levels of trichloroethylene. *Environ Mol Mutagen* 2022;63(8-9):423-428.
 36. Zhang J, Wang W, Pei Z et al. Mutagenicity Assessment to Pesticide Adjuvants of Toluene, Chloroform, and Trichloroethylene by Ames Test. *Int J Environ Res Public Health* 2021;18:8095.
 37. Irvin-Barnwell EA, Benson KM, Lu M et al. Environmental Toxins Found Historically in the Polycythemia Vera Cluster Area and their Potential for Inducing DNA Damage. *J Environ Anal Toxicol* 2021;8(1):10.4172/2161-0525.1000551.
 38. De Guzman K, Stone G, Yang AR et al. Drinking Water and the Implications for Gender Equity and Empowerment: A Systematic Review of Qualitative and Quantitative Evidence. *Int J Hygiene Environ Health* 2022;247:114044.
 39. Golka K, Böthig R, Weistenhöfer W et al. Occupation-related cancer in urology – Current Knowledge Including Environmental Medical Aspects. *Urologie* 2022;61(11):1198-1207. [Abstract in English, article in German].
 40. Jung K, Khan A, Mocharnuk R et al. Clinical Encounter with Three Cancer Patients Affected by Groundwater Contamination at Camp Lejeune: A Case Series and Review of the Literature. *J Med Case Reports* 2022;16:272.
 41. Georgakopoulou R, Fiste O, Sergentanis TN et al. Occupational Exposure and Multiple Myeloma Risk: An Updated Review of Meta-Analyses. *J Clin Med* 2021;10: 4179.
 42. Odotola MK, Benke G, Fritschi L et al. A Systematic Review and Meta-Analysis of Occupational Exposures and Risk of Follicular Lymphoma. *Environ Res* 2021;197:110887.