

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: Color Additive Petition submitted pursuant to 21 U.S.C. § 379e seeking amended color additive regulations to remove FDA’s approval of three carcinogenic solvents

Dear Dr. Muldoon Jacobs:

Petitioners submit this 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 make, mark, or color 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. § 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 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 2 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
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 humans	<ul style="list-style-type: none">• Liver effects

Trichloro-ethylene	<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 extracting resins from spices to make color additives and marking produce (see Table 2).

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

FDA approved uses	Ethylene dichloride	Methylene chloride	Trichloro-ethylene
Annatto extract (color)	30 ppm	30 ppm	30 ppm
Paprika oleoresin*(color)	30 ppm	30 ppm	30 ppm
Turmeric oleoresin* (color)	30 ppm	30 ppm	30 ppm
Ink to mark produce		No residue	
* Oleoresin is semisolid extract composed of resin and essential or fatty oil obtained by evaporation of the solvents used in their production.			

We have not identified foods or beverages in the U.S. that contain any of these carcinogenic solvents resulting from the allowable uses listed in Table 2, but since labelling is not required, there is no way to tell without rigorous testing. In addition, we have no evidence that FDA knows about current usage of any of these chemicals.

These solvents are likely to be present in food. For example, FDA analyzed 70 foods for volatile organic compounds (VOCs) including ethylene dichloride and trichloroethylene and detected them.¹

Notwithstanding the other risks posed by 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 color additive regulations to eliminate their uses.

I. About the Delaney Clause

Since 1960, the FFDCFA has stated that a “color additive shall be deemed unsafe, and shall not be listed, for any use which will or may result in ingestion of all or part of such additive, if the additive is found by the Secretary to induce cancer when ingested by man or animal, or if it is found by the Secretary, after tests which are appropriate for the evaluation of the safety of additives for use in food, to induce cancer in man or animal” (21 U.S.C. § 379e(b)(5)(B)).

¹ Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. J Agric Food Chem 2003; 51:8120-8127.

This requirement, known as the Delaney Clause, is a bright line drawn by Congress that carcinogens are not safe to use in food.² This statutory requirement has not been altered in the intervening half-century.

II. FDA Recognizes These Three Chemicals as Carcinogens

FDA itself already recognizes that these substances are carcinogenic.

FDA considers **ethylene dichloride** 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 their unacceptable toxicity or their deleterious environmental effect.”^{3,4} Yet, illogically, FDA permits ethylene dichloride to be used to manufacture of color additives. 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, “Forestomach cancer, hemangiosarcoma, breast cancer, uterine cancer and respiratory cancer were found in rats or mice after gavage treatment.”⁵ It also says, “possible human carcinogen (IARC 2B).”⁶ This entry references IARC and National Cancer Institute (NCI), now identified as an NTP⁷) study.⁸

FDA proposed a rule in 1977 to amend the color additive regulations by deleting trichloroethylene from the list of permissible solvents in certain color additives,⁹ based on studies by NCI showing the chemical caused cancer in laboratory animals. It stated,

“Having evaluated the available data, 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.

² 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)).

³ 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>.

⁴ 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>.

⁵ 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.

⁶ Ibid.

⁷ 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>.

⁸ 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.

⁹ FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene. 42 Fed. Reg. 49464 (September 27, 1977).

376(b)(5)(B) (i), its use in the production of a color additive may no longer be approved.”¹⁰
[emphasis added]

The cancer evidence on **trichloroethylene** also led FDA¹¹ 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;
- 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.¹² 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).¹³

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 be adulterated and subject to regulatory action, based on an NTP inhalation study in mice and exposure estimates from its use in hair sprays.¹⁴ Yet it continues to be allowed in food.

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

All three chemical have been tested as directed by the Department of Health and Human Services’ (HHS) and found to induce cancer in animals.¹⁵ 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 Three Chemicals is Widely Recognized by Authoritative Bodies

¹⁰ FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene. 42 Fed. Reg. 49464 (September 27, 1977).

¹¹ FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).

¹² FDA. Withdrawal of Certain Pre-1986 Proposed Rules; Final Action. 56 Fed. Reg. 67440 (December 30, 1991).

¹³ FDA. Food Additives Permitted for Direct Addition to Food for Human Consumption: Acesulfame Potassium. 68 Fed. Reg. 75411 (December 31, 2003).

¹⁴ 21 CFR 700.19.

¹⁵ See Appendices 1 and 3 for details.

- The U.S. Report on Carcinogens recognizes the carcinogenicity of all three 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 **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.¹⁶
- IARC recognizes the carcinogenicity of all three chemicals. Specifically, it designates one as Group 1, or “carcinogenic to humans” (**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.¹⁷ 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.¹⁸ The U.S. President’s Cancer Panel described IARC’s monographs on carcinogenesis as “the ‘gold standard’ in evaluating evidence on cancer-causation.”¹⁹ (See Appendix 3 Parts 2 and 3 for more details.)
- EPA recognizes the carcinogenicity of all three chemicals. Specifically, it designates one as carcinogenic to humans (**trichloroethylene**), one as a probable human carcinogen (**ethylene dichloride** (1,2-dichloroethane), and one as likely to be carcinogenic to humans (**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.²⁰
- ATSDR recognizes the carcinogenicity of all three chemicals. It has completed Tox Profiles for **methylene chloride**²¹ and **trichloroethylene**,²² and has issued a Tox Profile draft for public comment on **ethylene dichloride**,²³ all of which affirm the carcinogenicity of these

¹⁶ NTP, Report on Carcinogens, Fifteenth Edition, 2021. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html>.

¹⁷ See Appendix 3 Parts 2 and 3 for more details.

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

¹⁹ 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

²⁰ 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>.

²¹ ATSDR Toxicological Profile for Methylene Chloride. 2000. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

²² ATSDR. Toxicological Profile for Trichloroethylene. 2019. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.

²³ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

substances. It also recently published a **Systematic Evidence Map for methylene chloride**²⁴ 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 three 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).²⁵

The American Cancer Society lists all three chemicals on its “Known and Probable Human Carcinogens” webpage, based on “the determinations of other respected agencies” including IARC and NTP.²⁶

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

We note that, under the FFDCFA, there is no reason for FDA to conduct additional hazard analyses of the 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.²⁷ 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. **These Three Chemicals are Included in Color Additive Regulations**

FDA allows these chemicals to be used as solvents in its color additives regulations at 21 CFR §§ 73.30, 73.345, 73.615, and 73.1. In its 1977 proposal to amend the color additive regulations to remove provisions for trichloroethylene referenced previously, FDA made clear that the Delaney Clause applied to chemicals used in the production of a color additive.²⁸

A color additive is defined in [21 CFR § 70.3](#) Definitions paragraph (f):

“A color additive is any material, not exempted under section 201(t) of the act, that is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source and that, when added or applied to a food, drug, or cosmetic or to the human body or any part thereof, is capable (alone or through reaction with

²⁴ ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022.

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

²⁵ OEHHA, Proposition 65, accessed on April 18, 2023, at <http://www.oehha.ca.gov/prop65.html>.

²⁶ 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>.

²⁷ FDA. Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. 83 Fed. Reg. 50490 (October 9, 2018).

²⁸ FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene. 42 Fed. Reg. 49464 (September 27, 1977).

another substance) of imparting a color thereto. ...”

Paragraph (m) of this same section defines diluent:

“The term diluent means any component of a color additive mixture that is not of itself a color additive and has been intentionally mixed therein to facilitate the use of the mixture in coloring foods, drugs, or cosmetics or in coloring the human body. The diluent may serve another functional purpose in the foods, drugs, or cosmetics, as for example sweetening, flavoring, emulsifying, or stabilizing, or may be a functional component of an article intended for coloring the human body.”

Section 201(t) of the FFDCA states in paragraph (1):

“The term “color additive” means a material which— (A) is a dye, pigment, or other substance made by a process of synthesis or similar artifice, or extracted, isolated, or otherwise derived, with or without intermediate or final change of identity, from a vegetable, animal, mineral, or other source, and (B) when added or applied to a food, drug, or cosmetic, or to the human body or any part thereof, is capable (alone or through reaction with other substance) of imparting color thereto; except that such term does not include any material which the Secretary, by regulation, determines is used (or intended to be used) solely for a purpose or purposes other than coloring.”

These chemicals are listed in the color additive regulations (see Appendices 1 and 4).

Specifically, ethylene dichloride, methylene chloride, and trichloroethylene appear in 21 CFR Part 73, “Listing of Color Additives Exempt from Certification,” Subpart A, “Foods,” specifically under §73.30, “Annatto extract,” §73.345, “Paprika oleoresin,” and §73.615, “Turmeric oleoresin.” They are used as extractants or solvents in preparing those color additives exempt from certification. Each of those sections states that the color additive shall contain no more residue of the solvent than is permitted for the corresponding solvent in spice oleoresins.

In addition, methylene chloride appears in 21 CFR Part 73, “Listing of Color Additives Exempt from Certification,” Subpart A, “Foods,” specifically under § 73.1, “Diluents in color additive mixtures for food use exempt from certification,” paragraph (b)(ii) “Inks for marking fruits and vegetables.”

VII. All Three Chemicals Are Present in Food²⁹

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 three chemicals are present in food, although not necessarily from their uses to produce color additives.

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.³⁰ The study followed up on Clean Label Projects’s 2020 study that found methylene chloride in 10 of 25

²⁹ This section is not meant to be an exhaustive review of the literature but instead provides examples of key studies illustrating that these carcinogens are present in food.

³⁰ Clean Label Project. More Methylene Chloride! April 2023. https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper_3_2.pdf.

(40%) samples of decaffeinated coffees tested.³¹ 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 Market, 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 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 decaffeination of coffee, extracting hops and spices, from packaging, the storage environment, contaminated water used in production or processing, as products of combustion, from chlorination of processing water, or microwaving.³²

Ethylene dichloride was found in turmeric coloring in sampling done in Japan in the 1990s,³³ but we are not aware of similar but more recent testing, or testing in the U.S.

FDA analyzed 70 foods for VOCs including ethylene dichloride, and trichloroethylene and detected them in at least some foods. 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.³⁴

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 three chemicals to be hazardous air pollutants.³⁵ Hazardous air pollutants are those known to cause cancer and other serious health impacts.³⁶
- EPA determined that uses of two of these chemicals, methylene chloride and trichloroethylene, 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

³¹ Clean Label Project. Decaf Coffee: Our Point of View. 2020. <https://cleanlabelproject.org/wp-content/uploads/CLP-Decaf-Coffee-White-Paper.pdf>.

³² Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. J Agric Food Chem 2003; 51:8120-8127,

³³ Uematsu Y, Hirata K, Suzuki K et al. Survey of Residual Solvents in Natural Food Additives by Standard Addition Head-Space GC. Food Add Contam 2002;19(4):335-342.

³⁴ Fleming-Jones ME and Smith RE. Volatile Organic Compounds in Foods: A Five Year Study. J Agric Food Chem 2003; 51:8120-8127,

³⁵ 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>.

³⁶ EPA. [Hazardous Air Pollutants](https://www.epa.gov/haps). Last updated on February 9, 2023. <https://www.epa.gov/haps>.

neurotoxicity and liver effects.³⁷

- EPA also designated ethylene dichloride (1,2-dichloroethane) as a high priority for evaluation, and it is currently undergoing risk evaluation.³⁸ 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.³⁹
- 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.⁴⁰
- 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.⁴¹
- EPA has established reference doses (RfDs) for 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.⁴²
 - 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).⁴³ EPA assigns a

³⁷ [EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health](https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-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.

³⁸ EPA. [EPA Finds Trichloroethylene Poses an Unreasonable Risk to Human Health](https://www.epa.gov/chemicals-under-tsca/epa-finds-trichloroethylene-poses-unreasonable-risk-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](https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/risk-evaluation-for-1-2-dichloroethane) (Last updated on May 25, 2023) .

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> and 88 Fed. Reg. 28284.

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> and 88 Fed. Reg. 74712.

⁴² EPA. Integrated Risk Information System (IRIS) Glossary. Last updated 1/27/2023. https://sor.epa.gov/sor_internet/registry/termreg/searchandretrieve/glossariesandkeywordlists/search.do;jsessionid=VYQEuB3zwOSBOnxibuUp7aYNm18mPOKW8YyMXjY6P_kKAGKsV55F!-1457352436?details=&vocabName=IRIS%20Glossary&filterTerm=Reference%20dose&checkedAcronym=false&checkedTerm=false&hasDefinitions=false&filterTerm=Reference%20dose&filterMatchCriteria=Contains.

⁴³ EPA. IRIS. Dichloromethane. Last updated 11/18/2011. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=70.

“high” confidence in the oral RfD.⁴⁴

- 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.⁴⁵ EPA assigns a “high” confidence in the RfD.⁴⁶
- For ethylene dichloride, EPA has not established a RfD.⁴⁷ 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.⁴⁸ 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).⁴⁹ 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.⁵⁰

The consumer, community, and occupational exposures that may result from the use of these solvents 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 in the production of color additives and/or diluents in color additive mixtures for marking food because their uses are not safe pursuant to the Delaney Clause.

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

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

⁴⁴ EPA. IRIS. Chemical Assessment Summary. Dichloromethane. Last revised 11/18/2011. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0070_summary.pdf.

⁴⁵ EPA. IRIS. Trichloroethylene. Last updated 9/28/2011. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=199.

⁴⁶ EPA. IRIS. Chemical Assessment Summary. Trichloroethylene. Last revised 9/28/2011. https://iris.epa.gov/static/pdfs/0199_summary.pdf.

⁴⁷ EPA. IRIS. 1,2-Dichloroethane. https://iris.epa.gov/ChemicalLanding/&substance_nمبر=149.

⁴⁸ ATSDR. Minimal Risk Levels (MRLs) for Hazardous Substances. Last reviewed 6/21/2018. <https://www.atsdr.cdc.gov/mrls/index.html>.

⁴⁹ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comments. January 2022. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

⁵⁰ Dorsey ER, Zafar M, Lettenberger SE et al. Trichloroethylene: An Invisible Cause of Parkinson’s Disease? J Parkinson’s Disease 2023;13:203-218.

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

Appendix 4 presents the specific changes we seek in the color 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 color 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.

Pursuant to 21 C.F.R 70.19(q), petitioners request a waiver of the color additive petition fees and deposit requirements. The petitioners are non-profit organizations and individuals who submit this petition because it is in the public interest to protect public health by reducing carcinogenic exposures. Waiver of the fee under these circumstances promotes the public interest by removing a financial barrier that would otherwise serve as a deterrent to such efforts.

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 Three 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 § 71.1

Appendix 3 Reports on the Carcinogenicity of 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 Color Additive Regulations

Part 1: Requested changes to 21 CFR § 73.1(b)(1)(ii)

Part 2: Requested changes to 21 CFR § 73.1(a)(1)(ii)

Part 3: Requested changes to 21 CFR § 73.345

Part 4: Requested changes to 21 CFR § 73.615

Appendix 5 List of References

Appendix 1
Three Substances Permitted Under Color 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)
Ethylene dichloride/1,2-Dichloroethane	107-06-2	<p>§ 73.30 Annatto extract – Ethylene dichloride listed as a food-grade extractant.</p> <p>§ 73.345 Paprika oleoresin – lists ethylene dichloride as an extraction solvent that may be used.</p> <p>§ 73.615 Turmeric oleoresin – lists ethylene dichloride as an extraction solvent that may be used.</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>§ 73.1 Diluents in color additive mixtures for food use exempt from certification – inks for marking fruits and vegetables</p> <p>§ 73.30 Annatto extract – Methylene chloride listed as an extractant.</p> <p>§ 73.345 Paprika oleoresin – lists methylene chloride as an extraction solvent that may be used.</p> <p>§ 73.615 Turmeric oleoresin – lists methylene chloride as an extraction solvent that may be used.</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>§ 73.30 Annatto extract – Trichloroethylene listed as a food-grade extractant.</p> <p>§ 73.345 Paprika oleoresin – lists trichloroethylene as an extraction solvent that may be used.</p> <p>§ 73.615 Turmeric oleoresin – lists trichloroethylene as an extraction solvent that</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>

	may be used.	IARC: Carcinogenic to Humans (Group 1) (2014) CA Prop 65 Carcinogen (1988) NTP Study: Carcinogenic (mice (both sexes)); inadequate in male rats, no evidence in female rats (1990) NTP Study: Inadequate (1988) FDA: Proposed Rules to Remove Trichloroethylene due to tests finding it induces cancer (1977) NTP Study: Carcinogenic – Positive (mice (both sexes)); negative/inconclusive in rats (1976)
<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)</p> <p>See next page for references.</p>		

Sources for Appendix 1:

Ethylene Dichloride

- a. ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.
- b. 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.]
- c. OEHHA. Proposition 65. Ethylene Dichloride (1,2-Dichloroethane). 2023. <https://oehha.ca.gov/proposition-65/chemicals/ethylene-dichloride-12-dichloroethane>.
- d. 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.
- e. 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>.
- f. 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

- g. 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>.
- h. IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 243. [Includes methylene chloride.] <https://publications.iarc.fr/547>.
- i. EPA. IRIS Chemical Assessment Summary. Dichloromethane (CASRN 75-09-2). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0070_summary.pdf.
- j. ATSDR Toxicological Profile for Methylene Chloride. 2000. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
- k. ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.
- l. FDA. Cosmetics; Ban on the Use of Methylene Chloride as an Ingredient of Cosmetic Products. 54 Fed. Reg. 27328 (June 29, 1989), p. 27330.
- m. OEHHA. Proposition 65. Dichloromethane (Methylene Chloride), 2023. <https://oehha.ca.gov/proposition-65/chemicals/dichloromethane-methylene-chloride>.
- n. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Dichloromethane, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloromethane.pdf>.
- o. 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

- p. 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->

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- q. ATSDR. Toxicological Profile for Trichloroethylene. 2019. <https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=173&tid=30>.
 - r. EPA. IRIS Chemical Assessment Summary. Trichloroethylene (CASRN 79-01-6). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0199_summary.pdf.
 - s. EPA. Toxicological Review of Trichloroethylene. EPA/635/R-09/011F, 2011. https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0199tr/0199tr.pdf.
 - t. HHS, NTP. Report on Carcinogens, Fifteenth Edition, Trichloroethylene, 2021. <https://ntp.niehs.nih.gov/ntp/roc/content/profiles/trichloroethylene.pdf>.
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 - v. IARC. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. Volume 106. 2014. <https://publications.iarc.fr/130>
 - w. OEHHA. Proposition 65, Trichloroethylene. 2023. <https://oehha.ca.gov/proposition-65/chemicals/trichloroethylene>.
 - x. 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>.
 - y. 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>.
 - z. FDA. Trichloroethylene: Removal from Food Additive Use. 42 Fed. Reg. 49465 (September 27, 1977).
 - aa. FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene. 42 Fed. Reg. 49464 (September 27, 1977).
 - bb. 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 § 71.1

A. Name and Pertinent Information Concerning the Color Additive

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

Additive name	Molecular formula	Molecular Weight (g/mol)	CAS No.	UNI No	Synonyms
Ethylene dichloride /1,2-Dichloroethane	C2H4Cl2	98.96	107-06-2	55163IJI47	1,2-dichloroethane; EDC; ethane, 1,2-dichloro; alpha,beta-dichloroethane
Methylene chloride/ Dichloromethane		84.93	75-09-2	588X2YUY0 A	dichloromethane; methane, dichloro
Trichloroethylene/ TCE	C2HCl3	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/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/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/55163IJI47>, <https://precision.fda.gov/uniisearch/srs/unii/588X2YUY0A>, <https://precision.fda.gov/uniisearch/srs/unii/290YE8AR51>.

B. The Amount of the Color Additive Proposed for Use

None. We are asking FDA to remove ethylene dichloride, methylene chloride, and trichloroethylene from the color additive regulations because they cause cancer in animals and/or humans and therefore are not permissible.

C. Methods

We are asking FDA to remove ethylene dichloride, methylene chloride, and trichloroethylene from the color additive regulations because they cause cancer in animals and/or humans and therefore are not permissible.

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

D. Full reports of investigations made with respect to the safety of the color additive.

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

E. Data/Information on Probable Exposure to Ethylene Dichloride, Methylene Chloride, and Trichloroethylene

We are asking FDA to remove ethylene dichloride, methylene chloride, and trichloroethylene from the color additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. Therefore, this petition proposes to eliminate the probable dietary consumption of these chemicals from current levels and reduce the cumulative effect of the dietary intake.

As a result, no data/information on probable exposure is needed. See cover letter for additional information related to exposure.

F. Proposed Tolerances and Other Limitations on the Use of the Color Additives, if Required

We are asking FDA to remove ethylene dichloride, methylene chloride, and trichloroethylene from the color additive regulations because they cause cancer in animals and/or humans and therefore are not permissible.

As a result, no proposed tolerances or other limitations on their use are needed.

G. If Exemption from Batch Certification is Requested

We are asking FDA to remove ethylene dichloride, methylene chloride, and trichloroethylene from the color additive regulations because they cause cancer in animals and/or humans and therefore are not permissible. No additional exemption from batch certification is requested. Annatto extract, paprika oleoresin, and turmeric oleoresin should continue to be exempt from batch certification.

H. Proposed Changes to the Original Regulations

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

I. Request for Fee Waiver

Pursuant to 21 C.F.R 70.19(q), petitioners request a waiver of the color additive petition fees and deposit requirements. The petitioners are non-profit organizations and individuals who submit this petition because it is in the public interest to protect public health by reducing exposure to carcinogens. They have no financial interests in ethylene dichloride, methylene chloride, trichloroethylene, or any of the alternatives that may benefit from removing this color additive from the market.

J. Environmental review component

This color 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 ethylene dichloride, methylene chloride, and trichloroethylene in the color additive regulations as described in Section H 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 three ethylene dichloride, methylene chloride, and trichloroethylene is not an essential to make colors and, more broadly, the color additives are not essential.

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

1. Ethylene dichloride

According to § [73.30](#), other food-grade extractants may be used to make annatto extract, including acetone and isopropyl alcohol. Although methylene chloride and trichloroethylene are also used, we exclude those since they are subjects under this petition.

According to § [73.345](#), other extraction solvents may be used to produce paprika oleoresin, including acetone, ethyl alcohol, and isopropyl alcohol. We exclude methylene chloride and trichloroethylene, also listed, since they are subjects of this petition.

2. Methylene Chloride

According to § [73.1](#), many other substances can be used in inks for marking fruits and vegetables, such as acetone and alcohol (SDA-3A).115

According to § [73.30](#), other food-grade extractants may be used to make annatto extract, including acetone and isopropyl alcohol. Although ethylene dichloride and trichloroethylene are also used, we exclude those since they are subjects under this petition.

According to § [73.345](#), other extraction solvents may be used to produce paprika oleoresin, including acetone, ethyl alcohol, and isopropyl alcohol. We exclude ethylene dichloride and trichloroethylene, also listed, since they are subjects of this petition.

3. Trichloroethylene

According to § [73.30](#), other food-grade extractants may be used to make annatto extract, including acetone and isopropyl alcohol. Although ethylene dichloride and methylene chloride

are also used, we exclude those since they are subjects under this petition.

According to § [73.345](#), other extraction solvents may be used to produce paprika oleoresin, including acetone, ethyl alcohol, isopropyl alcohol, and methyl alcohol. We exclude ethylene dichloride and methylene chloride, also listed, since they are subjects of this petition.

Appendix 3

Reports on the Carcinogenicity of 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. Ethylene Dichloride

FDA identifies ethylene dichloride (1,2-dichloroethane) as a Class 1 solvent that should not be used to manufacture drugs.⁵¹ 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.”⁵²

It also says, “possible human carcinogen (IARC 2B).” This entry references IARC and the 1978 NCI (now available through NTP⁵³) study.

B. 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).⁵⁴

⁵¹ 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>.

⁵² FDA. Appendix 4: Toxicological Data for Class I 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.

⁵³ NTP. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. TR-55, 1978. <https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr055>.

⁵⁴ FDA. Food Additives Permitted for Direct Addition to Food for Human Consumption: Acesulfame Potassium. 68 Fed. Reg. 75411 (December 31, 2003).

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.⁵⁵ 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 issues and to defer any action on the food uses of methylene chloride.⁵⁶ Over three decades have passed since then and FDA must now take action on all food uses of methylene chloride listed in the food and color additive regulations.

FDA justified its decision to defer action on the food 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, and that it knew of no indications of a hazard to the public health from other food uses. 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.⁵⁷

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.”⁵⁸

In addition, FDA’s 1985 risk estimates are outdated. For example, EPA’s cancer potency estimate updated in 2011 is five times greater than what FDA used in its 1985 estimate.⁵⁹

C. Trichloroethylene

In 1977, FDA issued several proposed rules regarding trichloroethylene that were prompted by a bioassay by the NCI (now listed as an NTP report⁶⁰) that found that the chemical caused cancer in rodents. FDA proposed to amend § 73.30 Annatto extract, § 73.345 Paprika oleoresin, and § 73.615 Turmeric oleoresin by deleting “trichloroethylene” from those sections. Each of those three regulations on color additives contain specifications permitting levels of solvent residue in the finished color additive that are no more “than is permitted for the corresponding solvents in spice oleoresins under applicable food additive regulations in Parts 170 through 189 of this chapter,” i.e., in § 173.290 Trichloroethylene.⁶¹

⁵⁵ 21 CFR 700.19.

⁵⁶ FDA, Cosmetics; Ban on the Use of Methylene Chloride as an Ingredient of Cosmetic Products. 54 Fed. Reg. 27328 (June 29, 1989), p. 27330.

⁵⁷ 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)).

⁵⁸ FDA. Food Additive Regulations; Synthetic Flavoring Agents and Adjuvants. 54 Fed. Reg. 27328 (June 29, 1989).

⁵⁹ 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 FR 51551, December 18, 1985.

⁶⁰ NTP. Carcinogenesis Bioassay of Trichloroethylene. Technical Report 2.

<https://ntp.niehs.nih.gov/publications/reports/tr/000s/tr002>.

⁶¹ FDA. Annatto Extract, Paprika Oleoresin, and Turmeric Oleoresin: Removal of Provisions for Trichloroethylene –

In a separate proposed rule in 1977, 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.⁶² 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 proceeding to final action.⁶³

Thus, uses of trichloroethylene remain permitted.

In 2010, FDA implied that trichloroethylene is no longer being used in either the coffee or oleoresin industries.⁶⁴ 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.

Proposed Rule. 42 Fed. Reg. 49464 (September 27, 1977). <https://www.regulations.gov/document/FDA-1975-P-0006-0003>.

⁶² 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>.

⁶³ 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>.

⁶⁴ 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.^{65,66} NTP prepares the ROC on behalf of the Secretary. The most recent ROC is the fifteenth edition issued in December 2021.⁶⁷

The ROC designated **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.”⁶⁸

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.”⁶⁹

B. National Toxicology Program Cancer Studies

NTP was established in 1978 by the Secretary of HHS (then called the Department of Health, Education,

⁶⁵ NTP. History of the Report on Carcinogens. <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/history>.

⁶⁶ 42 U.S.C. § 241.

⁶⁷ NTP. Fifteenth Report on Carcinogens, 2021. Last updated April 14, 2023. See <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc>.

⁶⁸ 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.

⁶⁹ 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.

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.⁷⁰ 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).⁷¹

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.”⁷²

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

⁷⁰ NTP. History & Milestones. <https://ntp.niehs.nih.gov/whoweare/history>.

⁷¹ NTP. Organization. <https://ntp.niehs.nih.gov/whoweare/organization>.

⁷² NTP. Cancer Evaluation Criteria. 2023. <https://ntp.niehs.nih.gov/whatwestudy/testpgm/cartox/criteria>.

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.⁷³ 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.⁷⁴ The most recent monograph was Volume 131 published in 2023.⁷⁵ Since it is part of WHO, we consider IARC to be a recognized authority, as noted elsewhere in this petition, FDA has previously cited IARC's determinations on carcinogenicity.

IARC designated **trichloroethylene** as “*carcinogenic to humans*” or **Group 1**. According to IARC:⁷⁶

“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:⁷⁷

“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 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.

⁷³ IARC. Mission. <https://www.iarc.who.int/iarc-mission/>.

⁷⁴ IARC. IARC Monographs – General Information. <https://monographs.iarc.who.int/home/iarc-monographs-general-information/>.

⁷⁵ IARC. Monographs available. <https://monographs.iarc.who.int/monographs-available/>.

⁷⁶ IARC, Preamble to the Monographs, p. 35, <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

⁷⁷ IARC, Preamble to the Monographs, p. 35, <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

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:⁷⁸

“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.*”⁷⁹ 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.⁸⁰ 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 three chemicals that are the subject of this petition as carcinogens. A chemical is designated a **carcinogen** by one of four mechanisms^{81,82}:

1. **Labor Code.** Proposition 65 includes chemicals identified in California Labor Code section

⁷⁸ IARC, Preamble to the Monographs, p. 36, 2019. <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

⁷⁹ IARC, Preamble to the Monographs, p. 31-34, 2019. <https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf>.

⁸⁰ OEHHA, Proposition 65, 2023. <http://www.oehha.ca.gov/prop65.html>.

⁸¹ OEHHA, How chemicals are added to the Proposition 65 list, 2023. <https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list>.

⁸² OEHHA, Proposition 65 in Plain Language, 2023. <http://www.oehha.ca.gov/prop65/background/p65plain.html>.

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 did not designate any of the three chemicals 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 65.⁸³ 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 three chemicals to be carcinogenic, none were designated as carcinogens through 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 three chemicals were designated as carcinogens through this mechanism.

D. U.S. Environmental Protection Agency

EPA was established in 1970 by President Richard Nixon to protect human health and the environment.⁸⁴ 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.⁸⁵ EPA's IRIS classified **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.

EPA also evaluates the risk of chemicals under the Toxic Substances Control Act TSCA to determine whether they present an unreasonable risk to public health or the environment under the conditions of use.⁸⁶ EPA has completed risk evaluations for **trichloroethylene** and **methylene chloride** and

⁸³ OEHHA, Proposition 65, Carcinogen Identification Committee. Undated. <https://oehha.ca.gov/proposition-65/carcinogen-identification-committee>. Also see Cal. Health & Safety Code § 25249.8.

⁸⁴ EPA. EPA History. Last updated on April 17, 2023. <https://www.epa.gov/history>.

⁸⁵ 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>.

⁸⁶ 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>.

determined that they pose unreasonable risks to human health, in part because of their cancer risks.⁸⁷⁻⁸⁹ Ethylene dichloride (1,2-dichloroethane) is currently undergoing risk evaluation, having been identified as a high priority chemical in December 2019.⁹⁰

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.⁹¹ EPA has set the MCLG at **zero** for **ethylene dichloride (1,2-dichloroethane)**, **methylene chloride (dichloromethane)**, and **trichloroethylene** at least in part because of an increased risk of cancer.⁹²

Hazardous air pollutants are those known to cause cancer and other serious health impacts.⁹³ **Ethylene dichloride (1,2-dichloroethane)**, **methylene chloride (dichloromethane)**, and **trichloroethylene** are listed by EPA as **hazardous air pollutants**.⁹⁴

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

E. 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.⁹⁵ 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.⁹⁶ ATSDR has completed Tox Profiles for **methylene chloride**,⁹⁷ and **trichloroethylene**,⁹⁸ and has issued a Tox Profile draft for

⁸⁷ 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>.

⁸⁸ 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>.

⁸⁹ 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.

⁹⁰ 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>.

⁹¹ EPA. How EPA Regulates Drinking Water Contaminants. Last Updated November 2, 2022.

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

⁹² 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>.

⁹³ EPA. Hazardous Air Pollutants. Last updated on February 9, 2023. <https://www.epa.gov/haps>.

⁹⁴ 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

⁹⁵ ATSDR. <https://www.atsdr.cdc.gov/>. Last updated May 10, 2023.

⁹⁶ ATSDR. Toxicological Profile for Benzene. 2007.

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

⁹⁷ ATSDR Toxicological Profile for Methylene Chloride. 2000.

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

⁹⁸ ATSDR. Toxicological Profile for Trichloroethylene. 2019.

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

public comment on **ethylene dichloride**⁹⁹ which affirm the carcinogenicity of these substances. It also recently published a **Systematic Evidence Map for methylene chloride**¹⁰⁰ which provides an overview of new evidence published since the Tox Profile was published which continues to affirm the carcinogenicity of methylene chloride.

⁹⁹ ATSDR. Toxicological Profile for 1,2-Dichloroethane. Draft for Public Comment. 2022.
<https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=592&tid=110>.

¹⁰⁰ 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 three chemicals.

A. 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, 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.”¹⁰¹

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

¹⁰¹ 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>.

purposes, to regard 1,2-dichloroethane as if it presented a carcinogenic risk to humans.”¹⁰²

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 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.”¹⁰³

IARC concluded that “There is *sufficient evidence* in experimental animals for the carcinogenicity of 1,2-dichloroethane.”¹⁰⁴

In 1987, California’s OEHHA designated ethylene dichloride as a carcinogen based on the analysis of its independent committee of cancer experts.¹⁰⁵

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.”¹⁰⁶

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.”¹⁰⁷

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

¹⁰² 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>.

¹⁰³ 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.]

¹⁰⁴ Ibid.

¹⁰⁵ OEHHA. Ethylene dichloride (1,2-Dichloroethane). <https://oehha.ca.gov/proposition-65/chemicals/ethylene-dichloride-12-dichloroethane>.

¹⁰⁶ 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.

¹⁰⁷ 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>.

sexes.”¹⁰⁸

B. 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 chloride, EPA identified cancer from long-term exposure to methylene chloride.¹⁰⁹ 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.¹¹⁰

IARC first evaluated methylene chloride (dichloromethane) in 1987, designating it as “*possibly carcinogenic to humans* (Group 2B)” based on sufficient evidence in animals.¹¹¹

¹⁰⁸ 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>.

¹⁰⁹ 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>.

¹¹⁰ 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.

¹¹¹ IARC. Overall Evaluations of Carcinogenicity: An Updating of *IARC Monographs* Volume 1 to 42. 1987, p. 62, 194. <https://publications.iarc.fr/139>.

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.”¹¹²

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).¹¹³

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.¹¹⁴

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.”¹¹⁵

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

¹¹² IARC. Some Chemicals Used as Solvents and in Polymer Manufacture – Volume 110, 2016, p. 243. [Includes methylene chloride.] <https://publications.iarc.fr/547>.

¹¹³ Ibid.

¹¹⁴ EPA. IRIS Chemical Assessment Summary. Dichloromethane (CASRN 75-09-2). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0070_summary.pdf.

¹¹⁵ ATSDR Toxicological Profile for Methylene Chloride. 2000, p. 153. <https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

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.”¹¹⁶

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.”¹¹⁷

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.¹¹⁸

In 1988, California’s OEHHA designated methylene chloride as a carcinogen based on the analysis of its independent committee of cancer experts.¹¹⁹

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 1989.¹²⁰

In a 1986 Technical Report, NTP stated:

¹¹⁶ ATSDR. Systematic Evidence Map for Methylene Chloride. October 2022, p. 8
<https://www.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=234&tid=42>.

¹¹⁷ 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>.

¹¹⁸ 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>.

¹¹⁹ OEHHA. Dichloromethane (Methylene Chloride). <https://oehha.ca.gov/proposition-65/chemicals/dichloromethane-methylene-chloride>.

¹²⁰ HHS, NTP. Report on Carcinogens, Fifteenth Edition, Dichloromethane, 2021.
<https://ntp.niehs.nih.gov/ntp/roc/content/profiles/dichloromethane.pdf>.

“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.”¹²¹

C. 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 to identifying non-cancer risks, EPA identified risks for cancer.¹²² 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.”¹²³

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.¹²⁴ 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.”¹²⁵

¹²¹ 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>.

¹²² 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>.

¹²³ 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.

¹²⁴ Ibid

¹²⁵ EPA, Risk Evaluation for Trichloroethylene, EPA Document #740R18008, 2020, pp. 251-252.

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 were sufficient evidence from human studies that trichloroethylene exposure can cause kidney cancer in humans. There is also some evidence of an association between trichloroethylene exposure and non-Hodgkin’s lymphoma in humans.”¹²⁶

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.”¹²⁷

Trichloroethylene is also listed in the current (15th) U.S. Report on Carcinogens as:

https://www.epa.gov/sites/default/files/2020-11/documents/1_risk_evaluation_for_trichloroethylene_tce_casrn_79-01-6.pdf.

¹²⁶ATSDR. Toxicological Profile for Trichloroethylene. 2019, p. 4.

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

¹²⁷ EPA. IRIS Chemical Assessment Summary. Trichloroethylene (CASRN 79-01-6). Carcinogenicity Assessment Last Revised 2011. https://iris.epa.gov/static/pdfs/0199_summary.pdf.

“*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.”¹²⁸

It was first listed in 2000.¹²⁹

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

“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.”¹³⁰

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.”¹³¹

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.”¹³² In 1979 IARC concluded, “There is *limited evidence* that trichloroethylene is carcinogenic in mice.”¹³³

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

¹²⁸ HHS, NTP. Report on Carcinogens, Fifteenth Edition, Trichloroethylene, 2021.

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

¹²⁹ Ibid.

¹³⁰ 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.

¹³¹ Ibid.

¹³² 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>.

¹³³ 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>.

“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.”¹³⁴

In 1988, California’s OEHHA designated trichloroethylene as a carcinogen based on the analysis of its independent committee of cancer experts.¹³⁵

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 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.”¹³⁶

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.”¹³⁷

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

¹³⁴ IARC. Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents. Volume 106. 2014.

<https://publications.iarc.fr/130>.

¹³⁵ OEHHA. Trichloroethylene. <https://oehha.ca.gov/proposition-65/chemicals/trichloroethylene>.

¹³⁶ 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>.

¹³⁷ 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>.

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.”¹³⁸

¹³⁸ 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 three 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:

- 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: 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.¹³⁹

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.

¹³⁹ 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
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. Ethylene Dichloride

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

B. Methylene Chloride

Only one additional study on the ability of methylene chloride to cause or promote cancer was identified, which is also described under trichloroethylene, and 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 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 trichloroethylene was one of 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 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 study¹⁴⁰ 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.

C. 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, 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 trichloroethylene was one of 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 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*

¹⁴⁰ 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.

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,"¹⁴¹ 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 trichloroethylene was 1.07,

¹⁴¹ 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>.

indicating a slightly 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.

- 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. *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.*

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 cells¹⁴²], 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.”

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 oncoprotein¹⁴³] 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 histones¹⁴⁴) 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.

¹⁴² Thapa R, Wilson GD. The Importance of CD44 as a Stem Cell Biomarker and Therapeutic Target in Cancer. *Stem Cells Int* 2016;2016:2087204.

¹⁴³ 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.

¹⁴⁴ NIH National Center for Biotechnology Information. HDAC1 histone deacetylase 1. <https://www.ncbi.nlm.nih.gov/gene/3065>.

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.

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 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. Methylene chloride and trichloroethylene induced a significant amount of DNA damage in hematopoietic cells compared to the control. Methylene chloride induced significant effects at the 10 nM concentration and TCE at 100 nM. A dose-dependent relationship for 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, population-level prevalence of lifetime exposure to ten carcinogens, including 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 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 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, Sergentanis 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. 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 Color Additive Regulations

Part 1: Requested changes to 21 CFR § 73.1(b)(1)(ii)

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER A--GENERAL
PART 73 – LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION
Subpart A—Foods

Sec. 73.1 Diluents in color additive mixtures for food use exempt from certification.

[...]

(b) Special use - (1) Diluents in color additive mixtures for marking food –

[...]

(ii) *Inks for marking fruit and vegetables.* Items listed in paragraph (a) of this section and the following:

Substances	Definitions and specifications	Restrictions
Acetone	As set forth in N.F. XI	No residue.
Alcohol, SDA-3A	As set forth in 26 CFR pt. 212	Do.
Benzoin	As set forth in U.S.P. XVI	
Copal, Manila		
Ethyl acetate	As set forth in N.F. XI	Do.
Ethyl cellulose	As set forth in sec. 172.868 of this chapter	
Methylene chloride		Do.
Polyvinylpyrrolidone	As set forth in sec. 173.55 of this chapter	
Rosin and rosin derivatives	As set forth in sec. 172.615 of this chapter	
Silicon dioxide	As set forth in sec. 172.480 of this chapter	Not more than 2 pct of the ink solids.
Terpene resins, natural	As set forth in sec. 172.615 of this chapter	
Terpene resins, synthetic	Polymers of [alpha]- and [beta]-pinene	

Part 2: Requested changes to 21 CFR § 73.30(a)(1)(ii)

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER A--GENERAL PART 73 – LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

Subpart A—Foods

Sec. 73.30 Annatto extract.

(a) Identity. (1) The color additive annatto extract is an extract prepared from annatto seed, *Bixa orellana* L., using any one or an appropriate combination of the food-grade extractants listed in paragraph (a)(1)(i) and (ii) of this section:

(i) Alkaline aqueous solution, alkaline propylene glycol, ethyl alcohol or alkaline solutions thereof, edible vegetable oils or fats, mono- and diglycerides from the glycerolysis of edible vegetable oils or fats. The alkaline alcohol or aqueous extracts may be treated with food-grade acids to precipitate annatto pigments, which are separated from the liquid and dried, with or without intermediate recrystallization, using the solvents listed under paragraph (a)(1)(ii) of this section. Food-grade alkalis or carbonates may be added to adjust alkalinity.

(ii) Acetone, ~~ethylene dichloride~~, hexane, isopropyl alcohol, methyl alcohol, ~~methylene chloride~~, ~~trichloroethylene~~.

(2) Color additive mixtures for food use made with annatto extract may contain only diluents that are suitable and that are listed in this subpart as safe in color additive mixtures for coloring foods.

(b) Specifications. Annatto extract, including pigments precipitated therefrom, shall conform to the following specifications:

(1) Arsenic (as As), not more than 3 parts per million; lead as Pb, not more than 10 parts per million.

(2) When solvents listed under paragraph (a)(1)(ii) of this section are used, annatto extract shall contain no more solvent residue than is permitted of the corresponding solvents in spice oleoresins under applicable food additive regulations in parts 170 through 189 of this chapter.

[...]

Part 3: Requested changes to 21 CFR § 73.345

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER A--GENERAL
PART 73 – LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

Subpart A—Foods

Sec. 73.345 Paprika oleoresin.

(a) Identity. (1) The color additive paprika oleoresin is the combination of flavor and color principles obtained from paprika (*Capsicum annuum* L.) by extraction, using any one or a combination of the following solvents:

Acetone

Ethyl alcohol

~~Ethylene dichloride~~

Hexane

Isopropyl alcohol

Methyl alcohol

~~Methylene chloride~~

~~Trichloroethylene~~

The definition of paprika oleoresin in this paragraph is for the purpose of identity as a color additive only, and shall not be construed as setting forth an official standard for paprika oleoresin under section 401 of the act.

(2) Color additive mixtures made with paprika oleoresin may contain as diluents only those substances listed in this subpart as safe and suitable in color additive mixtures for coloring foods.

(b) Specifications. Paprika oleoresin shall contain no more residue of the solvents listed in paragraph (a)(1) of this section than is permitted of the corresponding solvents in spice oleoresins under applicable food additive regulations in parts 170 through 189 of this chapter.

[...]

Part 4: Requested changes to 21 CFR § 73.615

TITLE 21--FOOD AND DRUGS CHAPTER I--FOOD AND DRUG
ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES SUBCHAPTER A--GENERAL
PART 73 – LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

Subpart A—Foods

Sec. 73.615 Turmeric oleoresin.

(a) Identity. (1) The color additive turmeric oleoresin is the combination of flavor and color principles obtained from turmeric (*Curcuma longa* L.) by extraction using any one or a combination of the following solvents:

Acetone

Ethyl alcohol

~~Ethylene dichloride~~

Hexane

Isopropyl alcohol

Methyl alcohol

~~Methylene chloride~~

~~Trichloroethylene~~

The definition of turmeric oleoresin in this paragraph is for the purpose of identity as a color additive only, and shall not be construed as setting forth an official standard for turmeric oleoresin under section 401 of the act.

(2) Color additive mixtures made with turmeric oleoresin may contain as diluents only those substances listed in this subpart as safe and suitable in color additive mixtures for coloring foods.

(b) Specifications. Turmeric oleoresin shall contain no more residue of the solvents listed under paragraph (a)(1) of this section than is permitted for the corresponding solvents in spice oleoresins under applicable food additive regulation in parts 170 through 189 of this chapter.

[...]

Appendix 5 List of References

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